Natural Health Products (NHPs) in Pregnancy and Lactation: A Review of the Landscape and Blueprint for Change

by

Jean-Jacques Dugoua HBSc ND

A thesis submitted in conformity with the requirements for the degree of Doctorate of Philosophy (PhD)
Graduate Department of Pharmaceutical Sciences
Leslie Dan Faculty of Pharmacy
University of Toronto

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Abstract

**Introduction:** Based on the perceived risk to newborns and pregnancy outcomes associated with certain drugs, women may be hesitant to prescribe and take drugs during pregnancy. In cases like these, pregnant women may seek treatment using natural health products (NHPs) as alternatives to drugs. Unfortunately, evidence of safety in pregnancy and lactation is unknown for many NHPs.

**Objectives:** To review the present state of evidence on the safety of NHPs during pregnancy and lactation. To create a new system to validate evidence on NHPs during pregnancy and lactation designed to affect medical decision.

**Methodology:** NHPs were systematically reviewed and in some cases, meta-analyzed for evidence of safety during pregnancy and lactation.

**Results:** In total, 79 NHPs were systematically reviewed and 2 NHPs were meta-analyzed in order to determine the evidence of safety in pregnancy and lactation. Despite the presence of data (72/79 NHPs in pregnancy and 53/77 NHPs in lactation), the quality of the data was generally poor. Using evidence-based medicine principles, a new system of evaluating evidence was established for studies involving NHPs in pregnancy and lactation. A number of NHPs were identified as being of potential risk in pregnancy. A number of NHPs were identified as potentially being apparently safe in pregnancy and lactation. Blue cohosh is of potential concern for harm in pregnancy given an apparent dose-dependant relationship.

**Conclusion:** There is a large knowledge gap on the safety of NHPs in pregnancy, even more so in lactation. The new system for evaluating NHP safety in pregnancy and lactation will require
validation. In order to improve the knowledge gap, future studies are proposed on NHPs in pregnancy and lactation as part of the newly formed MotherNature research network.
Acknowledgments

I would like to thank the Leslie Dan Faculty of Pharmacy Sciences at the University of Toronto for funding a large part of my PhD via the Shoppers Drug Mart Ontario Graduate Student Scholarship, the William Knapp Buckley Award OSOTF sponsored by the Ontario College of Pharmacists and other graduate scholarships. I would also like to thank the Sick Kids Foundation for funding via the Complementary and Alternative Health Care and Pediatrics Masters Scholarship.

I would like to thank my supervisors Dr. Koren, Dr. Einarson and Dr. Mills for their guidance, ideas, constructive criticism and knowledge. I would also like to thank Ms. Adrienne Einarson, Ms. Myla Moretti and all the fellows and researchers at the Motherisk program.

I would like to thank my mother Dorothea Dugoua, sister Marie-Chantal Dugoua and nieces Maya and Chloe Lavoye for their love and support.

Lastly and most importantly, I would like to thank my wife who one day will benefit from the material in this dissertation when she is pregnant.
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Chapter 1

According to the United States National Institutes of Health (NIH), all pregnancies involve a certain degree of risk to both mother and baby\(^1\). Pregnant women and their newborns are at higher risk depending on their age (too young or too old), body weight (overweight or underweight), previous pregnancy complications (stillbirth, miscarriage, preterm labour) and pre-existing health conditions (high blood pressure, HIV/AIDS)\(^1\).

Drug exposure is another concern to pregnant women, more specifically to newborns, due to the associated-risk of fetal malformations with certain pharmaceutical drugs. A number of drugs taken during gestation can lead to fetal malformations, such as thalidomide\(^2\), retinoids (Acutane®), methotrexate, angiotensin converting enzymes (ACE) inhibitors, coumarin derivatives, diethylstilbestrol, tetracycline, warfarin and others\(^3\). Based on the risk of teratogenesis associated with certain drugs, women and their health care providers may be hesitant to prescribe and take drugs during pregnancy.

In a study on the pharmaceutical drug use of 295 pregnant women, 37% of these women reported non-compliance with their existing drug regimen due to hesitations on drug use during pregnancy\(^4\). In a study of 100 women taking antidepressants during pregnancy compared to 100 controls, 15% of antidepressant users chose to discontinue their medication despite receiving evidence-based reassuring information of relative safety\(^5\). The researchers concluded that pregnant women appeared to fear taking antidepressants due to a perceived risk to their newborn\(^5\). A study conducted at the Motherisk Program of the Sick Kids Hospital found that a significant number of pregnant women had misperceptions and distorted information regarding the potential teratogenic risk of drugs and chemicals\(^6\). The study also found that pregnant women assigned an unrealistically high risk to medications not known to be teratogenic\(^6\). The decision whether to continue or discontinue a drug during pregnancy is a complex decision for women and their healthcare provider. In cases where women chose to discontinue their drug use during pregnancy, they often seek natural health products (NHPs) as alternatives to pharmaceutical drugs.
In many parts of the world, women still use herbal medicines for fertility and childbirth even when attended by Western medicine\textsuperscript{7,8}. In traditional Chinese medicine, there are approximately 20 herbal medicines used in pregnancy\textsuperscript{9}. Research into native North Americans medicinal plants has found over 100 plants used as abortifacients and approximately 350 plants used as female gynecological aids\textsuperscript{10}. European settlers in North America became aware of native medicinal plants and began using them clinically with their patients. Once assessed as clinically effective, these herbal medicines were described by Eclectic physicians in \textit{King’s American Dispensatory}\textsuperscript{11}. \textit{Vitex agnus-castus} has over 2000 years of history for helping women with fertility, regulating menstruation and being a lactation aid\textsuperscript{12-14}. Raspberry leaf was used by the Cherokee for labor pains and by the Cree and Cherokee to slow uterine bleeding\textsuperscript{10,11}. A common herbal preparation, called \textit{partus preparatus}, has a long history of being administered to pregnant women 3-6 weeks prior to delivery; \textit{partus preparatus} includes a combination of the following herbs: \textit{Actea (Cimicifuga) racemosa}, \textit{Mitchella repens}, \textit{Viburnum prunifolium}, \textit{Caulophyllum thalactroides}, \textit{Aralia nudicaulis}, \textit{Rubus idaeus}, \textit{Leonurus cardiaca}, \textit{Nepeta cataria} and \textit{Gelsemium sempervirens}\textsuperscript{11,15,16}. Women also use herbal medicines in many parts of the world for contraception and women’s health\textsuperscript{8}. In the Philippines, 60 medicinal plants were identified as being abortifacients and over 130 plants were identified as emmenagogues, i.e. herbs that stimulation menstruation\textsuperscript{17}.

Lactation is another area where pregnant women use herbal medicines. Breast milk is beneficial to the baby, however, some women may have difficulties with lactation where one study showed that 15\% of Canadian new mothers reported insufficient milk supply\textsuperscript{18}. Women have used herbal medicines to support lactation worldwide for thousands of years. These herbal medicines are called galactagogues, i.e. herbs that promote lactation. Over 400 medicinal plants have been used ethnomedically or recorded in the literature as being galactagogues\textsuperscript{19}. \textit{Trigonella foenum-graecum} has historically been used in Europe and North Africa for its ability to stimulate milk production\textsuperscript{20,21}. \textit{Galega officinalis} has been used in Europe to promote lactation\textsuperscript{11,20}. The traditional medicine of India, called Ayurveda, has identified galactagogues such as \textit{Rauwolfia serpentina}, \textit{R. oreogiton} and \textit{R. volkensii}\textsuperscript{22}. Traditional Chinese medicine has identified a number of galactagogues, such as \textit{Astragalus membranaceus}, \textit{Taraxacum mongolicum}, \textit{Tetrapanax papyrfera}, \textit{Liquidambar taiwani}a and \textit{Ligusticum chuaniong}\textsuperscript{23}. 
In Canada, under Schedule I of the Natural Health Products Regulation, NHPs are defined as: a) a plant or plant material, an alga, a bacterium, a fungus, or non-human animal material, b) an extract of item ‘a’, c) a vitamin, d) an amino acid, e) an essential fatty acid, f) a synthetic duplicate of items ‘b-e’, g) a mineral or h) a probiotic. According to a 2002 survey by the Natural Health Products Directorate (NHPD), the division of Health Canada responsible for registering and monitoring NHPs in Canada, 71% of Canadians have used some form of NHP. Twenty nine percent (29%) feel that NHPs are natural and safe or better than conventional medications.

One of the challenges of studying NHPs is that the Natural Health Products Regulation has lumped a large and diverse group of medicinal products into one category: NHPs. When evaluating therapeutic indications, vitamins have been studied more extensively in comparison to herbal medicines (Appendix A). In pregnancy and lactation research, this is also the case (Appendix A). For example, folic acid has been studied more often in pregnancy versus black cohosh. The main advantage of lumping this broad category into one group is that it allows for comparison of NHPs versus pharmacological agents. The disadvantage, however, is that NHPs are a heterogeneous group and that will entail limitations with interpretations and conclusions.

Although the NHPD survey does not provide data on the use of NHPs by Canadians during pregnancy, it is believed that NHP use by pregnant women is quite common, somewhere between 7% and 55%. A survey in the United States (US) of 734 pregnant women found that 7.1% of women used herbal medicines during their pregnancy; most commonly Echinacea, St. John’s wort and ephedra. A survey in the US of 242 pregnant women found that 9.1% of women used herbal supplements during their pregnancy and 7.5% of women used these at least weekly. In this study, the most commonly used herbs during pregnancy were garlic, aloe, chamomile, peppermint, ginger, Echinacea, pumpkin seeds and ginseng. A survey in the US of 150 pregnant women found that 13% of women used dietary supplements during their pregnancy; most commonly Echinacea, pregnancy tea and ginger. A survey in South Africa of 229 pregnant women found that 55% of women reported ingesting herbal medicines during pregnancy. According to the Motherisk Program in Toronto (Canada), over 6,000 callers every year seek advice about the safe use of NHPs, such as vitamin A, Echinacea and St. John’s wort, during their pregnancy.
Although hesitant, some healthcare providers may recommend herbs during pregnancy. A survey of 242 medical and naturopathic doctors and students reported that only one physician actually recommended a herbal product to a pregnant patient whereas 49% of the naturopathic doctors felt comfortable doing so32. According to a survey of midwives in the US, between 45% to 93% of midwives will prescribe some form of NHP to women during their pregnancy33. Of the midwives who used herbal preparations, 64% used blue cohosh, 45% used black cohosh, 63% used red raspberry, 93% used castor oil and 60% used evening primrose oil33.

In addition to intended NHP use during pregnancy, there is a concern of accidental NHP exposure by the mother and fetus. Conception is usually not planned and it is probable that a pregnant woman may be exposed to teratogenic factors (birth defects) when she is not aware of her pregnancy34. For example, the herbal medicines chastetree and evening primrose oil are frequently used by women of child-bearing age for the treatment of premenstrual syndrome (PMS) and cystic mastalgia35-38. Although there is no evidence demonstrating that chastetree or evening primrose oil cause birth defects, it is conceivable that an unknowingly pregnant woman could expose the fetus to chastetree or evening primrose oil during the first trimester of her pregnancy with unknown consequences.

NHP use by pregnant women and women of childbearing age could be due to a paradoxical response to the decreased use of prescribed medications during pregnancy for fear of teratogenicity or simply seeking alternative medicines. For many women, NHPs may seem a reasonable alternative to pharmaceutical drugs as the lay media often portrays natural medicines as “safe”. Despite the prevalent use of NHPs by pregnant women, there is very little published evidence with regards to the safety or efficacy of NHPs during pregnancy. Many modern and classic texts warn against the use of herbal medicines during pregnancy or lactation for up to one-third of the products listed in their monographs39-42. However, most resources provide little information on the data used to evaluate reproductive toxicity apart from reports of historical use of herbs as abortifacients or uterine stimulants or animal data of genotoxicity or teratogenicity39-42.

During pregnancy, a woman is in a unique physiological state in comparison to a non-pregnant woman. For example, during pregnancy the following occur: blood volume increases43, renal physiology changes44 and drug metabolism is altered45. Risk of adverse events in pregnancy is
sensitive to the timing of the intervention. A drug or NHP intervention in the first trimester of pregnancy, where the majority of organogenesis occurs, is more likely to increase the risk of malformations versus an intervention in the third trimester. A drug or NHP intervention in the third trimester of pregnancy is more likely to have an impact on the due date, premature birth incidence and delivery complications. When treating patients during pregnancy, clinicians must be aware that they are exposing both the mother and the fetus to a drug or NHP. In many cases, it is unclear if the drug, NHP or their metabolites reach the fetus. During lactation, women impart a number of benefits to their newborn by breastfeeding, such as a lower risk of diarrhea\textsuperscript{46} and otitis media\textsuperscript{47}, and improved cognitive function\textsuperscript{48} to name a few. Drugs taken by the mother may cross into breast milk and into the newborn. There have been cases where drugs taken by the mother have caused morbidity and death in the newborn via transmission into breast milk\textsuperscript{49,50}. In some cases, pregnant women inclined toward NHP treatments during their pregnancy and lactation will seek the advice of clinicians. In other cases, women may seek information on the Internet. With knowledge that the evidence of NHP safety in pregnancy and lactation is perceived to be poor, clinicians are faced with a dilemma on how to counsel these women. Clinicians would benefit from a system that allows them to evaluate evidence of NHP safety in pregnancy and lactation and that affects their medical decision. At this time, no such system exists.

The objective of this dissertation was to review the present state of evidence on the safety of NHPs during pregnancy and lactation, and to create a new system to validate evidence on NHPs during pregnancy and lactation designed to affect medical decision. These objectives will involve systematic reviews of the scientific literature for evidence of NHP safety during pregnancy and lactation, and meta-analyses provided there is sufficient data to be extracted. Another objective of this dissertation will be to evaluate potential NHP treatments for high-risk pregnancies, such as gestational diabetes.

Based on these objectives, the working hypotheses of this dissertation were as follows:

1. There is evidence of safety associated with the use of NHPs during pregnancy.

2. There is evidence of safety associated with the use of NHPs during lactation.

3. There is evidence of effective NHP interventions for high-risk pregnancies.
As part of my PhD, I have published 14 manuscripts: 8 manuscripts as first author (Chapters 3-10), 3 manuscripts as second author (Appendix B), 2 manuscripts not relevant to the topic of this dissertation (Appendix C) and 1 textbook as second author where I conducted the large majority of the work (Chapter 2 and Appendix A).
2 Herbal Medicines in Pregnancy and Lactation – An Evidence-Based Approach

Chapter 3 is extracted from the textbook cited below, which was published by Taylor & Francis. Given the length of this textbook, the 75 systematic reviews from this textbook are listed in Appendix A instead of the main body of text for this thesis. The full reference is as follows:


2.1 Reference and Manuscript

Chapter 3: Methods

In keeping with the principles of evidence-based practise, I have endeavored to identify all the relevant literature on the specific health products examined. The search strategy employed systematic searching of the following databases:

- AltHealth Watch
- AMED
- CINAHL
- Cochrane Database of Systematic Reviews
- Cochrane CENTRAL Controlled Trials Database
- E-Psyche
- DARE
- MedLine
The MeSH terms used for searching included ‘pregnancy’, ‘lactation’, and ‘breastfeeding’. For individual health products, we searched using both the common and Latin names, and where appropriate, we searched using known synonyms. In the case of a well-known active ingredient or constituent, this term was also used in the search for its safety during pregnancy and lactation. The principal databases used were:

- Pubmed
- Cochrane Trial Registry (CENTRAL) and Cochrane Review Database
- AMED
- CINAHL
- E-Psyche

To ensure that reports, trials, and other forms of evidence were not overlooked owing to the variety of common names for each individual herb, e.g. *Panax ginseng* is also known as ren shen in traditional Chinese medicine, the following additional databases were consulted:

- www.naturalstandard.com
- www.naturaldatabase.com
- The Complete German Commission E Monographs by the American Botanical Council

Each relevant journal was collected and referenced in our database. The nature of the findings and the grade of evidence were then assessed and compiled in our final report.

The grade of evidence for indications was evaluated as follows:
<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
</table>
| A     | Very Strong Scientific Evidence  
Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis. |
| B1    | Strong Scientific Evidence  
Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs). |
| B2    | Good scientific evidence  
Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methods. |
| C     | Fair Scientific Evidence  
Statistically significant evidence of benefit from one or more cohort studies OR outcome studies. |
| D     | Weak Scientific Evidence  
Evidence from case series. |
| E     | INDIRECT and/or Clinical evidence  
Evidence from case reports OR expert opinion OR laboratory studies. |
| F     | Historical or traditional evidence  
Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups. |
The level of evidence for harm was evaluated as follows:

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Very Strong scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence from one or more systematic reviews or RCTs.</td>
</tr>
<tr>
<td>1b</td>
<td>Strong Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence from one or more cohort studies OR case control study.</td>
</tr>
<tr>
<td>1c</td>
<td>Good Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence from one or more case series.</td>
</tr>
<tr>
<td>2</td>
<td>Fair Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on case reports.</td>
</tr>
<tr>
<td>3</td>
<td><em>In vitro</em> scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
</tr>
<tr>
<td>4</td>
<td>Theoretical evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on scientific theory OR expert opinion.</td>
</tr>
<tr>
<td>5</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>No available information.</td>
</tr>
</tbody>
</table>
2.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized the book entitled “Herbal Medicines in Pregnancy and Lactation – An Evidence-based Approach”. Along with Ed Mills, I developed the methodology and the evidence based scale used to evaluate harm/safety in pregnancy and lactation (Chapter 3). I conducted and drafted all 75 systematic reviews listed in this book, i.e., Chapters 4-6. Although not the first author, I performed the vast majority of work on this textbook. Dan Perri, a pharmacist and physician, drafted Chapter 2. Paul Richard Saunders, a herbologist and naturopathic doctor, drafted Chapter 1. Dan Perri, Ed Mills and I drafted the Preface, which serves as the introduction to the book.

2.3 Statement of significance and impact

To my knowledge, this is the first collection of this kind to specifically address the harm or safety of NHPs in pregnancy and lactation. Although it has often been suspected that the evidence of NHP use in pregnancy and lactation was poor, these systematic reviews have highlighted the large extent of the knowledge gap in this area of research. This book has highlighted a number of NHPs that are clearly not safe during pregnancy and lactation, that may be of minimal risk if taken at specific times in pregnancy and lactation, or that have an unknown impact. With respect to future study, these reviews have identified many potential areas were data are lacking and clinical study is required.

The methods section from this textbook is included to provide the rationale for this thesis. I applied the methods and evidence levels from this textbook to all future publications for assessing harm or safety in pregnancy. These levels of evidence could have a large scope of application in evidence-based medicine.
3 Probiotic Safety in Pregnancy: a Systematic Review and Meta-analysis of Randomized Controlled Trials of *Lactobacillus, Bifidobacterium, and Saccharomyces spp.*

Published as a manuscript in the Canadian Journal of Obstetrics and Gynecology. The full reference for the manuscript is as follows:


3.1 Reference and manuscript

Title: Probiotic Safety in Pregnancy: a Systematic Review and Meta-analysis of Randomized Controlled Trials of *Lactobacillus, Bifidobacterium, and Saccharomyces spp.*

Jean-Jacques Dugoua, HBSc ND PhD (Cand.), Marcio Machado PhD, Xu Zhu MSc, Xin Chen HBSc, Gideon Koren MD FABMT FRCPC, Thomas R. Einarson PhD
Abstract

Our objective in this study was to review systematically the evidence for safety of Lactobacillus, Bifidobacterium and Saccharomyces spp. during pregnancy and to conduct a meta-analysis of randomized controlled trials (RCTs). Eleven databases were searched from inception to September 2007 for RCTs of probiotic use during pregnancy. Two independent reviewers searched databases. Random-effects models combined data. Eleven studies on Lactobacillus and/or Bifidobacterium examined 1505 patients for four outcomes with no data heterogeneity; no miscarriage data were reported. Five studies reported Caesarean section outcomes (OR 0.88; 95% CI 0.65–1.19). Six studies reported birth weight (weighted difference 45 g; 95% CI:-181 to 271). Three studies reported gestational age (weighted difference 0.4 weeks; 95%CI-0.4 to 1.2). No malformations were reported in the probiotic group. No RCTs were available for Saccharomyces during pregnancy. Lactobacillus and Bifidobacterium had no effect on the incidence of Caesarean section, birth weight or gestational age. The safety of Saccharomyces during pregnancy is unknown.

Key Words: Pregnancy, probiotics, lactobacillus, bifidobacterium, saccharomyces

ABBREVIATIONS

BV bacterial vaginosis

CFU colony forming unit

LGG L. rhamnosus GG

RCT randomized controlled trial

TGF-β transforming growth factor β

INTRODUCTION

The use of natural health products during pregnancy is quite common, the prevalence of herbal medicine use during pregnancy being between 7% and 55%. A survey in the United States
found that between 45% and 93% of midwives had prescribed some form of natural health product to women during their pregnancy.⁵ A collection of 75 systematic reviews, published as a textbook on natural health products in pregnancy and lactation, concluded that evidence for their safety and efficacy during pregnancy and lactation was lacking.⁶

Probiotics, one group of natural health products, consist of live bacteria or non-pathogenic yeast that colonize the gastrointestinal tract and provide a health benefit to the host.⁷ Lactobacillus spp. and Bifidobacterium spp. were reported as the most commonly used probiotic strains.⁸ Saccharomyces spp. have also been reported as being commonly used.⁸

Lactobacillus spp. refers to a group of lactic acid-producing, Gram-positive rods that are obligate and facultative anaerobes.⁹ Lactobacillus species include L. acidophilus, L. bulgaricus, L. casei rhamnosus, L. delbrueckii, L. fermentum, L. plantarum, L. reuteri, L. rhamnosus GG, and L. sporogenes.¹⁰ Bifidobacterium spp. are anaerobic, rod-shaped, Gram-positive bacteria that normally colonize the human colon.¹¹ They constitute a predominant part of the anaerobic flora of the human colon and are the predominant intestinal organisms of breast-fed infants.¹¹ Bifidobacterium species include B. adolescentis, B. animalis, B. bifidum, B. breve, B. infantis, B. lactis, and B. longum.¹² Saccharomyces spp. are a group of non-pathogenic probiotic yeast which includes S. bouardii and S. cerevisiae.¹³,¹⁴

Clinically, meta-analyses and systematic reviews of clinical trials have demonstrated a significant benefit of Lactobacillus spp., Bifidobacterium spp., and Saccharomyces spp. alone or in combination for the prevention of acute diarrhea,¹⁵ treatment of Clostridium difficile-associated diarrhea,¹⁶ prevention of traveller’s diarrhea,¹⁷ treatment of yeast vaginitis and bacterial vaginosis,¹⁸ treatment of acute diarrhea in children,¹³,¹⁹ and treatment of antibiotic-associated diarrhea in children.²⁰ Many studies varying in methodological quality have addressed the safe use and benefits of Lactobacillus spp., Bifidobacterium spp. or Saccharomyces spp. throughout pregnancy.²¹–²⁸ For example, L. rhamnosus GG was shown to be effective in the
prevention of atopic disease in newborns when administered to pregnant women\textsuperscript{21–27} and in the prevention of preterm labour.\textsuperscript{28}

There is an outstanding need to determine the safety of administering probiotics during pregnancy. A number of clinical indications for probiotic use, such as diarrhea, yeast vaginitis, and bacterial vaginosis, have mostly been assessed in non-pregnant women. If deemed to be of minimal risk, probiotics could be of therapeutic benefit to pregnant women for these clinical indications.

Our objective was to conduct a systematic review of the scientific literature for randomized controlled trials on the administration of \textit{Lactobacillus spp.}, \textit{Bifidobacterium spp.}, and \textit{Saccharomyces spp.} during pregnancy and to conduct a meta-analysis of these trials to provide more precise estimates of risk.

\textbf{METHODS}

For this systematic review, we included RCTs that assessed the effects of administering one or more of the three probiotic groups, i.e., \textit{Lactobacillus spp.}, \textit{Bifidobacterium spp.} or \textit{Saccharomyces spp.}, or placebo to pregnant women. The probiotics administered could have been given at any time during pregnancy, at any dose, in any form (i.e., capsule, tablet, liquid, food [yogourt]), for any condition (e.g., atopic disease, vaccine antibodies), and given for at least one week. We included only studies with data on birth weight, gestational age, or incidence of the following: Caesarean section, malformations (major or minor) or miscarriage. Non-English journal articles were included, but studies related to probiotic administration after birth or during lactation were excluded.

Institutional Review Board approval is not required for systematic reviews and/or meta-analyses at the authors’ institution.
In keeping with the principles of evidence-based practice, we endeavoured to identify and analyze the relevant RCTs that provided information on the safety of *Lactobacillus* spp., *Bifidobacterium* spp., and *Saccharomyces* spp. during pregnancy. Two independent reviewers systematically searched the following databases from their inception to September 2007: MEDLINE (1966-), OLDMEDLINE (1950–65), Cumulative Index to Nursing & Allied Health Literature (CINAHL) (1982-), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness (DARE), Allied and Complementary Medicine (AMED) (1985-), EMBASE (1980-), AltHealthWatch. To ensure that no RCTs were overlooked, the following additional databases were consulted: Complete German Commission E Monographs by the American Botanical Council, Natural Database, and Natural Standard. We also hand-searched the bibliographies of relevant studies and contacted experts in the field to identify RCTs that may remain unpublished.

The databases were searched using the following MeSH terms “lactobacillus,” “bifidobacterium,” “bifidobacteria,” “saccharomyces,” and each of these terms with “pregnancy.” After we obtained the peer-reviewed publications, wherever possible, two reviewers independently assessed eligibility on the basis of the full text papers. Third-party arbitration was used in the case of any disagreements regarding inclusion.

Two reviewers conducted data extraction independently and assessed the study quality of each publication using the checklist developed and validated by Downs and Black.29 The checklist uses the following criteria to evaluate quality: reporting, external validity, internal validity (bias and confounding/selection bias) and power.29 Reviewers were not blinded to authorship or journal name.

In cases where reviewer scores were within 10% of each other, reviewers discussed the differences in their quality evaluations and then established a consensus for the final scoring of
the publication. In cases where the difference in reviewer scores exceeded 10%, third party arbitration was used to address the differences between their quality evaluations and then to establish a consensus for the final scoring of the publication. Once scored, each publication was referenced in our database and tabulated (Table 1). Additionally, studies were assigned an evidence level for harm (Table 2). The evidence levels used in Table 2 are standardized and described further in previous publications.\textsuperscript{6,30-33}

When available, data on birth weight, gestational age and incidence of Caesarean section were extracted from the RCTs and tabulated. Data were combined using random effects meta-analytical models.\textsuperscript{34} In the case of Caesarean section data, incidences were pooled across the strata of 2 x 2 tables, and the odds ratio was calculated using a random effects meta-analytic model.\textsuperscript{34} In the case of birth weight and gestational age, the difference between treatment and placebo group means was calculated using a random effects model for continuous variables (i.e., weighted mean difference). For quality assurance purposes, data were examined using the chi-squared test\textsuperscript{34} and the $I^2$ test for heterogeneity.\textsuperscript{35} The statistical software used during this study was Review Manager (RevMan) Version 4.2 for Windows (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

**RESULTS**

In total, 55 human studies were extracted from the scientific literature on probiotics during pregnancy, of which 11 were RCTs (Table 1 and Figure 1). Two studies were excluded (Rinne et al. 2005 and 2006) as they were sub-group analyses of the Kallimaki et al. (2001) study. The Rautava et al. study\textsuperscript{26} was also a sub-group analysis of the Kalliomaki et al. (2001) study\textsuperscript{22}; however, it was included in the meta-analysis as it contained data on Caesarean section rates that were not presented in the Kalliomaki et al. (2001) study.\textsuperscript{22} Lastly, the Neri et al. (1993) study was excluded from meta-analysis as it did not contain any extractable data on pregnancy safety. No data on malformations and miscarriage incidence were available or suitable for meta-analysis.
Of the remaining eight RCTs included for meta-analysis, the probiotic intervention was of *Lactobacillus spp.* alone\(^{21,22,26,28,36}\) or in combination with *Bifidobacterium spp.*\(^{24,37,38}\) There were no RCTs on *Saccharomyces spp.* during pregnancy. A flow chart of extracted studies is presented in Figure 1.

Based on the reported Caesarean section outcomes, we found no evidence of publication bias using Begg-Mazumdar test (tau = 0.200, *P* = 0.624).\(^{39}\) Nonetheless, we cannot completely rule out the possibility of publication bias because of the small number of studies (K = 5) in our search guidelines that reported the incidence of Caesarean section.

The RCTs are summarized in Table 1. The findings from the RCTs are discussed individually. Results of the meta-analysis are presented at the end of the Results section.

**Systematic Review**

Abrahamsson et al.\(^{21}\) conducted a randomized controlled trial of 232 pregnant women with a family history of atopic disease.\(^{21}\) The women received oil droplets of *L. reuteri* ATCC 55730 (1x10\(^8\) CFU) or placebo daily from week 36 of gestation until expected delivery.\(^{21}\) At delivery, 227 women delivered healthy infants with no reports of malformations (major or minor), low birth weight, or preterm delivery.\(^{21}\) The infants were then directly administered *L. reuteri* or placebo for two years. At the end of the trial, the authors reported that infants treated with *L. reuteri* had significantly less IgE- associated eczema at two years of age and therefore may possibly have a reduced risk of developing later respiratory allergic disease.\(^{21}\)

Gueimonde et al. conducted a randomized controlled trial in 53 pregnant women with a family history of atopic disease.\(^{36}\) Pregnant women were administered an unreported daily dose of LGG or placebo from four weeks before the date of expected delivery until expected delivery.\(^{36}\) The objective was to study the effects of LGG or placebo on mother-infant *Bifidobacteria* transfer at
birth and the development of *Bifidobacteria* during the first weeks of life. At delivery, 53 women delivered infants with no reports of malformations (major or minor), low birth weight, or preterm delivery. At five days of age, infants whose mothers received LGG showed a significantly higher occurrence of *B. breve* and lower occurrence of *B. adolescentis* than those from the placebo group. LGG intake increased the *Bifidobacterial* diversity in infants and reduced the *Bifidobacterium* species similarity between mother and infant.

Kalliomaki et al. conducted a randomized controlled trial in 159 pregnant women with a family history of atopic disease. The women received either two capsules daily of LGG (1x10^10 CFU) or placebo from 2–4 weeks before the expected date of delivery until actual delivery. At delivery, 155 women delivered healthy infants with no reports of malformations (major or minor), low birth weight, or preterm delivery. After delivery, the infants received LGG or placebo directly for six months and were monitored to four years of age. At two years of age, the frequency of atopic eczema in the LGG group was half that of the placebo group (RR = 0.51; 95% CI 0.32–0.84). At four years of age, the frequency of atopic disease remained lower in the LGG group than in the placebo group (14/53 vs. 25/54; RR = 0.57; 95% CI 0.33–0.97).

Kaplas et al. conducted a small randomized controlled trial in a group of pregnant women participating in a cohort study on nutritional intake during pregnancy. At a mean of 13.8 ± 1.4 weeks’ gestation, pregnant women were randomized to received two capsules daily of LGG and *B. lactis* (1x10^9 CFU per capsule) or placebo until the end of their pregnancy. The groups were further divided into three: group 1 received the probiotic and dietary counselling, group 2 received the placebo and dietary counselling, and group 3 received the placebo. The pregnancies were uncomplicated and the infants were delivered at term; there were no reports of malformations (major or minor), miscarriages, low birth weight, or preterm delivery. Concentrations of linoleic (18:2n-6) and dihomo-e-linolenic acids (20:3n-6) in placental and umbilical cord samples taken at birth and up to 24 hours later were significantly higher (P < 0.05) in women given dietary counselling with probiotics than in women given dietary counselling and placebo or placebo alone.
Kukkonen et al. (2006) conducted a randomized controlled trial in a sub-group of 87 pregnant women already enrolled in the Kukkonen et al. (2007) atopic disease prevention trial previously discussed. The purpose of this study was to observe the effects, if any, of probiotic intake on vaccine antibody response in newborns. The pregnant women received the same dosing regimen pre- and post-pregnancy as discussed above in the Kukkonen et al. study. Infants followed Finland’s routine vaccination schedule to six months of age. At six months of age, there was no difference in antibody responses to diphtheria, tetanus or Haemophilus influenzae type b vaccination between probiotic and placebo groups.

Kukkonen et al. conducted a randomized controlled trial of 1223 pregnant woman with a family history of atopic disease. At 2–4 weeks before expected delivery, pregnant woman received one capsule twice daily of either placebo or a probiotic combination containing four strains: L. rhamnosus GG (5 x 10⁹ CFU), L. rhamnosus LC705 (5 x 10⁹ CFU), B. breve (2 x 10⁸ CFU) and Propionibacterium freudenreichii spp. Shermanii (2 x 10⁹ CFU). At delivery, there were no reports of malformations (major or minor) in the probiotic group, but three reports in the placebo group (0/610 and 3/613, respectively). There were 27 reports of preterm delivery in the probiotic group and 18 reports in the placebo group (27/610 and 18/613, respectively), and no reports of low birth weight. After delivery, infants received either an opened capsule of the probiotics administered to their mother and 20 drops of sugar syrup (0.8 g of galacto-oligosaccharides) or an opened capsule of placebo and 20 drops of sugar syrup without galacto-oligosaccharides daily for the first six months of life. Infants were monitored until two years of age. At three and six months of age, fecal analysis indicated that Lactobacillus spp. and Bifidobacterium spp. more frequently colonized the guts of probiotic supplemented infants. At two years of age, probiotic treatment was associated with a significant reduction in eczema and atopic eczema in treated infants compared with the placebo group.

Neri et al. conducted an open randomized trial of 64 women with bacterial vaginosis in their first trimester of pregnancy. Pregnant women were divided into three groups: group 1 received a
10–15 mL vaginal douche (inserted with a syringe) of commercially available yogourt containing *L. acidophilus* (> 1 x 10⁸ CFU per mL) with a pH < 4.5, group 2 received a large vaginal tampon soaked with 10–15 mL of 5% acetic acid before insertion, and group 3 received no treatment (control).⁴¹ Treatments were administered twice daily for seven days and then repeated one week later. The effect of the treatment was evaluated at four and eight weeks after completion of treatment by monitoring the presence or absence of BV criteria and patients’ subjective feelings.⁴¹ At four and eight weeks post treatment, the probiotic group had a significant absence of BV in comparison to both the acetic acid and control groups.⁴¹ The authors concluded that the continuous correction of both the vaginal pH and *Lactobacillus spp.* flora was crucial for normal vaginal ecology, and was responsible for the high treatment response rate.⁴¹

Nishijima et al. conducted a randomized controlled trial in 24 pregnant women near full term (35 weeks of gestation).²⁸ Pregnant women received either 120 g/day of fermented milk containing 1 x 10⁹ CFU of *L. johnsonii* or a placebo fermented milk for two weeks.²⁸ Vaginal fluid samples were collected before and after administration of the fermented milk. In the probiotic group, pathogenic bacteria such as *Gardnerella vaginalis* and *Corynebacterium spp.* were detected in four of the 12 subjects, but were undetectable after two weeks of probiotic administration.²⁸ In the placebo group, pathogenic bacteria were detected in three of the 12 subjects and remained present after two weeks of placebo treatment.²⁸ The authors concluded that oral administration of probiotics can restore the vaginal flora in pregnant women.²⁸ Since this study was published as a letter to the editor and was very brief, the authors did not provide any information on the birth outcomes in either group nor report any major or minor malformations.²⁸

Rautava et al.²⁶ conducted a sub-group analysis on 62 mother-infant pairs receiving either LGG or placebo as part of the Kalliomaki et al.²² study. Breast milk samples were analyzed for TGF-β concentration. Elevated levels of TGF-β are believed to enhance the ability of infants to produce specific IgA antibodies against dietary antigens and therefore, prevent atopic disease in breastfed infants.⁴² The amount of breast milk TGF-β in mothers receiving LGG was significantly superior to placebo, thereby suggesting that LGG increases the immunoprotective potential of breast milk when administered during pregnancy and lactation.²⁶
**Meta-analysis**

The primary pregnancy outcomes were Caesarean section rate, birth weight, and gestational age. Only one study reported the incidence of malformations; no malformations were reported in the probiotic group, while three cases with malformations were reported in the placebo group. In six of the eight RCTs, the probiotic interventions occurred at 32–34 weeks’ gestation, so data on miscarriage and malformation incidences were unlikely. Two studies were conducted in the first trimester and could therefore have provided data on miscarriage incidence; however, the authors did not report any incidences of miscarriage. The studies that contained data on Caesarean section, birth weight, and gestational age are presented in Tables 3, 4, and 5, respectively.

For the outcome of Caesarean section, the odds ratio (OR) was 0.88 (95% CI 0.65–1.19) (Figure 2). There was no evidence of heterogeneity in the data ($\chi^2 = 0.97, P = 0.915$; $I^2 = 0, P = 0.24$).

For the outcome of birth weight, the meta-analytic means were 3.609 kg (± 0.146 kg) in the probiotic group and 3.587 kg (± 0.122 kg) in the placebo group. Compared with placebo, there was a non-significant increase in birth weight of 45g ($P = 0.699$) associated with taking probiotics during pregnancy. The data did not display heterogeneity of effects ($\chi^2 = 0.46, P = 0.994$; $I^2 = 0, P = 0.334$).

For the outcome of gestational age, the meta-analytic means were 39.8 weeks (± 0.4 weeks) in the probiotic group and 39.2 weeks (± 0.5 weeks) in the placebo group. Compared with placebo, there was a non-significant increase in gestational age of 0.4 weeks ($P = 0.336$) associated with taking probiotics during pregnancy. The data did not display heterogeneity of effects ($\chi^2 = 0.79, P = 0.673$; $I^2 = 0, P = 0.804$).
**DISCUSSION**

Of the studies systematically reviewed, the majority rated well according to the quality checklist by Downs and Black\(^\text{29}\) (Table 1). Some methodological weaknesses were identified; for example, Gueimonde et al. did not report the dose of probiotics administered.\(^\text{36}\)

Given the poor quality of evidence typically found when researching natural health products during pregnancy, as observed in previous publications,\(^\text{6}\) the identification of 11 RCTs on use of probiotics during pregnancy is impressive. The studies were related to topics on atopic disease prevention, mother-to-infant microflora transfer, BV, placental transfer of fatty acids, and immunization.

Before a unifying statement can be made that probiotics are either safe or effective during pregnancy, it must be emphasized that probiotics constitute a group of microorganisms, and there may be differences between individual species. Three genera were reviewed in this study: *Lactobacillus, Bifidobacterium*, and *Saccharomyces*. The studies extracted in this review and meta-analysis relate only to the three specific probiotic strains studied. For example, since LGG was the most commonly studied *Lactobacillus sp.* intervention in pregnancy, it cannot be concluded that all *Lactobacillus spp.* will have the same clinical effect on atopic disease prevention or safety profile.

Another consideration when evaluating safety is the timing of the probiotic intervention during pregnancy. The majority of the RCTs were conducted between weeks 32–36 and delivery. A probiotic intervention at 32–36 weeks of gestation is unlikely to increase miscarriage risk or affect organogenesis. For example, it is difficult to conclude that the *L. reuteri* administered in the study of Abrahamsson et al.\(^\text{21}\) had any effect on gestational age: the intervention commenced one week before the beginning of what is considered full-term, i.e., the intervention was at week 36, and the normal full term for pregnancy is between weeks 37 and 42. Only Kaplas et al.\(^\text{37}\) and Neri et al.\(^\text{41}\) conducted studies in which probiotics were administered in the first trimester of
pregnancy. Despite there being no reports of miscarriages or malformations in these two studies, it is not possible to conclude that probiotics have no effect on miscarriage or malformations incidence until more RCTs are available for meta-analysis.

Of the 11 RCTs identified, only eight contained pregnancy outcome data for meta-analysis: Caesarean section rate, birth weight or gestational age.\textsuperscript{21,22,24,26,28,36–38} Administering LGG alone or in combination with \textit{L. rhamnosus, B. breve} and \textit{P. freudenreichii} spp. \textit{Shermanii} did not affect the incidence of Caesarean section (OR = 0.88; 95% CI 0.65–1.19). With respect to birth weight and gestational age, only mean values, and not incidences of low birth weight or preterm infants, were available. Administering \textit{L. reuteri} alone, LGG alone or in combination with \textit{B. lactis, L. rhamnosus, B. breve} and \textit{P. freudenreichii} spp. \textit{Shermanii} did not affect birth weight. Administering LGG alone or in combination with \textit{B. lactis} did not appear to have affected gestational age. Taking these probiotics appeared to have been related to a small and non-significant increase in birth weight of 45 g and a non-significant increase in gestational age of approximately three days (0.4 weeks). Even if these results were statistically significant, it is unlikely that these results would be judged as clinically relevant.

It could be argued that mean values of birth weight and gestational age were not ideal for evaluating pregnancy safety. The best basis for determining if a probiotic intervention is a risk factor for low birth weight or preterm delivery would have been the incidences of low birth weight infants and preterm deliveries in the probiotic and placebo groups. None of these data were available in the manuscripts extracted for meta-analysis. The corresponding authors were contacted to obtain these data, and, according to the authors who replied, the data were either not available or it was against the policy of their institutions to release any patient information (even anonymous information) outside their institution. We hope that these authors will publish their results in the future.

With respect to the results from the RCTs, there were a number of important clinical findings. LGG and \textit{L. reuteri} appear to play a role in decreasing the incidence of atopic disease in infants
up to four years of age. Since LGG and *L. reuteri* were also administered to the infants, it is not possible to conclude whether the observed prevention of atopic disease was due to the probiotics administered during pregnancy, those administered during infancy, or both. The most dramatic results with respect to atopic disease prevention were association with the administration of LGG. The less favourable results reported in the *L. reuteri* study may be due to methodological weaknesses in their study. Abrahamsson et al. used *L. reuteri* in a suspension of coconut (3/4) and peanut oil (1/4). Although the authors reported that the peanut oil contained < 0.005% peanut protein and unknown amounts of coconut protein, it is plausible that administering known allergens and hyper-sensitizing agents such as peanuts and coconut may have exacerbated the atopic condition tested. In fact, the intervention of *L. reuteri* would have to offset the familial susceptibility to atopic disease along with a repeated daily intake of an allergen and hyper-sensitizing agent. In the future, it would be more prudent for clinical studies of atopic disease to avoid using carrier solutions that are known allergens or hyper-sensitizing agents such as peanuts and coconut.

BV is a risk factor for prematurity and post-partum complications. *L. acidophilus* administered as a yogourt suppository appears to be a safe and effective treatment of BV in pregnancy. The continuous correction of both the vaginal pH and *Lactobacillus spp.* flora via the suppositories was believed by Neri et al. (1993) to be crucial for normal vaginal ecology and responsible for the high treatment rate.

LGG appears to affect the mother-infant bifidobacteria transfer at birth and bifidobacteria development later in life. Gueimonde et al. reported that LGG given at four weeks pre-delivery decreased *B. adolescentis* and increased *B. breve*. *B. adolescentis* is more frequently isolated from allergic infants than from healthy infants, and *B. breve* may prevent atopic disease in infants.

LGG and *B. lactis* may affect fatty acid transfer in the placenta, leading to higher placental concentrations of linoleic and dihomo-<wbr/>c-linolenic acids. The administration of LGG, *L.
rhamnosus, B. breve, and P. freudenreichii spp. Shermanii to pregnant mothers did not affect antibody responses to diphtheria, tetanus, or Haemophilus influenzae type b vaccination.\textsuperscript{38}

Lastly, the use of Saccharomyces spp. may be of concern during pregnancy because of reports about the implication of S. boulardii as an etiologic agent of invasive infection.\textsuperscript{46} A comprehensive review of the scientific literature reported 92 cases of Saccharomyces invasive infection.\textsuperscript{46} Clinically, Saccharomyces invasive infection was indistinguishable from an invasive candidiasis and had similar predisposing factors, such as intravascular catheter placement and antibiotic therapy.\textsuperscript{46} The review also reported that treatment with intravenous amphotericin B and fluconazole were effective therapeutic options.\textsuperscript{46} In our systematic review, no studies addressed Saccharomyces spp. as an intervention for pregnant women. Although the reported cases of Saccharomyces invasive infection were treatable, it is not prudent for Saccharomyces spp. to be administered to pregnant women, nor is it recommended.

**CONCLUSIONS**

The 11 studies of probiotic use in pregnancy that were reviewed were generally of good methodological quality and provided good evidence with respect to pregnancy. The meta-analysis did not indicate that administering certain strains of Lactobacillus spp. and Bifidobacterium spp. had any effect on Caesarean section rate, birth weight, or gestational age. Certain strains of Lactobacillus sp. and Bifidobacterium sp. may prevent atopic disease in infants when administered to their mothers in pregnancy. L. acidophilus yogourt suppositories are a safe and effective treatment of BV in pregnancy. LGG and B. lactis increased fatty acid transfer to the placenta. LGG, L. rhamnosus, B. breve, and P. freudenreichii spp. Shermanii administered to pregnant women did not affect antibody responses to diphtheria, tetanus or Haemophilus influenzae type b vaccination. At present, the safety of Saccharomyces spp. during pregnancy is unknown.
References


Figure 1. Probiotics in pregnancy flow chart

**Lactobacillus spp. (L. spp.)**
29 studies

**Bifidobacterium spp. (B. spp.)**
18 studies

**Saccharomyces spp.**
8 studies

Human studies extracted
55

36 non-RCTs excluded

11 RCTs
*L. spp. or L. spp. combined with B. spp.*

Excluded
2 - duplicate data
1 - no extractable data

8 RCTs

8 non-RCTs excluded

0 RCTs

RCT: randomized controlled trial

spp: species
Figure 2. Forest plot of Caesarean section outcomes for probiotic use during pregnancy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (random) 95% CI</th>
<th>W/Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamsen, 2007</td>
<td>11/114</td>
<td>15/113</td>
<td>13.05 0.70 [0.31, 1.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gueinno, 2006</td>
<td>3/29</td>
<td>4/24</td>
<td>3.45 0.58 [0.12, 2.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kukkonen, 2006</td>
<td>5/47</td>
<td>6/40</td>
<td>5.52 0.67 [0.19, 2.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kukkonen, 2007</td>
<td>75/451</td>
<td>79/453</td>
<td>73.95 0.94 [0.57, 1.54]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rautava, 2002</td>
<td>4/30</td>
<td>4/32</td>
<td>4.03 1.08 [0.24, 4.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>571</td>
<td>662</td>
<td>100.00 0.88 [0.65, 1.19]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 98 (Treatment), 108 (Control)
Test for heterogeneity: Chi² = 0.97, df = 4 (P = 0.91), I² = 0%
Test for overall effect: Z = 0.33 (P = 0.40)
Table 1. Randomized controlled trials of probiotics in pregnancy.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Intervention</th>
<th>Dosage (daily)</th>
<th>Results</th>
<th>Statistically significant</th>
<th>Quality Score</th>
<th>Evidence Grade (Table 2)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamsson et al. (2007)</td>
<td>232</td>
<td>Oil droplets of <em>L. reuteri</em> ATCC 55730 or placebo</td>
<td>$1 \times 10^6$ CFU</td>
<td>Treated infants had less IgE-associated eczema at 2 years of age than those from the placebo group.</td>
<td>Yes</td>
<td>87.1%</td>
<td>1a</td>
<td>Very strong scientific evidence</td>
</tr>
<tr>
<td>Gueimonde et al. (2006)</td>
<td>53</td>
<td>LGG or placebo</td>
<td>NA</td>
<td>Infants whose mothers received LGG showed a significantly higher occurrence of <em>B. breve</em> and lower occurrence of <em>B. adolescentis</em> than those from the placebo group</td>
<td>Yes</td>
<td>45.2%</td>
<td>1a</td>
<td>Good scientific evidence</td>
</tr>
<tr>
<td>Kalliomäki et al. (2001)</td>
<td>159</td>
<td>LGG or placebo</td>
<td>$1 \times 10^8$ CFU</td>
<td>At 2 years of age, the frequency of atopic eczema in the LGG group was half that of the placebo group. At 4 years of age, the frequency of atopic disease remained lower in the LGG group versus placebo</td>
<td>Yes</td>
<td>74.2%</td>
<td>1a</td>
<td>Very strong scientific evidence</td>
</tr>
<tr>
<td>Kaplas et al. (2007)</td>
<td>30</td>
<td>LGG or placebo</td>
<td>$1 \times 10^9$ CFU</td>
<td>Dietary counseling with probiotics resulted in higher concentrations of linoleic and dihomo-γ-linolenic acids compared with dietary counseling and placebo or with placebo alone</td>
<td>NA</td>
<td>51.6%</td>
<td>1b</td>
<td>Good scientific evidence</td>
</tr>
<tr>
<td>Author (year)</td>
<td>n</td>
<td>Intervention</td>
<td>Dosage (daily)</td>
<td>Results</td>
<td>Statistically significant</td>
<td>Quality Score</td>
<td>Evidence Grade (Table 2)</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kukkonen et al. (2006)</td>
<td>61</td>
<td>Probiotics and galactooligosaccharides, or a placebo</td>
<td>5 × 10^7 CFU or 2 × 10^6 CFU or 2 × 10^6 CFU</td>
<td>Probiotics may improve response to Hib immunization</td>
<td>Yes</td>
<td>83.9%</td>
<td>1a</td>
<td>Very strong scientific evidence.</td>
</tr>
<tr>
<td>Kukkonen et al. (2007)</td>
<td>925</td>
<td>Probiotics and galactooligosaccharides, or a placebo</td>
<td>5 × 10^7 CFU or 2 × 10^6 CFU or 2 × 10^6 CFU</td>
<td>Probiotic treatment showed no effect on the incidence of all allergic diseases by age 2 years but significantly prevented eczema and especially atopic eczema</td>
<td>Yes</td>
<td>87.1%</td>
<td>1a</td>
<td>Very strong scientific evidence.</td>
</tr>
<tr>
<td>Nishijima et al. (2005)</td>
<td>24</td>
<td>Fermented milk containing <em>L. johnsonii</em></td>
<td>10^6 CFU per ml</td>
<td>Oral administrations of probiotics can restore vaginal flora in pregnant women</td>
<td>Yes</td>
<td>29.0%</td>
<td>1a</td>
<td>Strong scientific evidence Small sample size</td>
</tr>
<tr>
<td>Rautava et al. (2002)</td>
<td>62</td>
<td>LGG or placebo</td>
<td>2 × 10^10 CFU</td>
<td>LGG increases the immunoprotective potential of breast milk when administered during pregnancy and lactation</td>
<td>Yes</td>
<td>51.6%</td>
<td>1a</td>
<td>Sub-group analysis of data from Kalliomaki et al. (2001)</td>
</tr>
</tbody>
</table>

n: sample size; LGG: *Lactobacillus rhamnosus GG*; CFU: colony-forming units
Table 2. Levels of evidence for harm

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>EVIDENCE</th>
</tr>
</thead>
</table>
| 1a    | **VERY STRONG SCIENTIFIC EVIDENCE**  
Statistically significant evidence from one or more systematic reviews or RCTs. |
| 1b    | **STRONG SCIENTIFIC EVIDENCE**  
Statistically significant evidence from one or more outcome studies OR cohort studies OR case control studies. |
| 1c    | **GOOD SCIENTIFIC EVIDENCE**  
Evidence from one or more case series. |
| 2     | **FAIR SCIENTIFIC EVIDENCE**  
Evidence based on case reports. |
| 3     | **IN VITRO SCIENTIFIC EVIDENCE**  
Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells. |
| 4     | **INDIRECT EVIDENCE**  
Evidence based on scientific theory OR expert opinion. |
| 5     | **UNKNOWN**  
No available information. |
Table 3. Results from studies reporting on the relationship between use of probiotics and Caesarean section

<table>
<thead>
<tr>
<th>Studies</th>
<th>Probiotic group</th>
<th></th>
<th>Placebo group</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-section</td>
<td>Vaginal</td>
<td>C-section</td>
<td>Vaginal</td>
<td></td>
</tr>
<tr>
<td>Abrahamsson et al. (2007)¹⁸</td>
<td>11</td>
<td>103</td>
<td>15</td>
<td>98</td>
<td>0.517</td>
</tr>
<tr>
<td>Gueimonde et al. (2006)³³</td>
<td>3</td>
<td>26</td>
<td>4</td>
<td>20</td>
<td>0.787</td>
</tr>
<tr>
<td>Kukkonen et al. (2007)¹²¹</td>
<td>75</td>
<td>376</td>
<td>79</td>
<td>374</td>
<td>0.814</td>
</tr>
<tr>
<td>Kukkonen et al. (2006)³⁵</td>
<td>5</td>
<td>42</td>
<td>6</td>
<td>34</td>
<td>0.776</td>
</tr>
<tr>
<td>Rautava et al. (2002)²³</td>
<td>4</td>
<td>26</td>
<td>4</td>
<td>28</td>
<td>0.780</td>
</tr>
<tr>
<td>Overall</td>
<td>98</td>
<td>573</td>
<td>108</td>
<td>554</td>
<td>0.413</td>
</tr>
</tbody>
</table>

Table 4. Results from studies reporting on the relationship between use of probiotics and birth weight in kilograms

<table>
<thead>
<tr>
<th>Studies</th>
<th>Probiotic group</th>
<th></th>
<th>Placebo group</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Abrahamsson et al. (2007)¹⁸</td>
<td>3.66</td>
<td>0.42</td>
<td>114</td>
<td>3.60</td>
<td>0.47</td>
</tr>
<tr>
<td>Kalliomaki et al. (2001)¹⁹</td>
<td>3.63</td>
<td>0.48</td>
<td>77</td>
<td>3.61</td>
<td>0.47</td>
</tr>
<tr>
<td>Kaplas et al. (2007)³⁴</td>
<td>3.80</td>
<td>0.14</td>
<td>10</td>
<td>3.71</td>
<td>0.16</td>
</tr>
<tr>
<td>Kukkonen et al. (2007)¹²¹</td>
<td>3.60</td>
<td>0.48</td>
<td>461</td>
<td>3.59</td>
<td>0.48</td>
</tr>
<tr>
<td>Kukkonen et al. (2006)³⁵</td>
<td>3.58</td>
<td>0.42</td>
<td>47</td>
<td>3.57</td>
<td>0.47</td>
</tr>
<tr>
<td>Nishijima et al. (2005)²⁵</td>
<td>2.80</td>
<td>0.39</td>
<td>12</td>
<td>2.97</td>
<td>0.34</td>
</tr>
<tr>
<td>Overall</td>
<td>3.51</td>
<td>0.39</td>
<td>721</td>
<td>3.51</td>
<td>0.4</td>
</tr>
</tbody>
</table>

SD: standard deviation; n: sample size
Table 5. Results from studies reporting on the relationship between use of probiotics and gestational age

<table>
<thead>
<tr>
<th>Studies</th>
<th>Probiotic group</th>
<th>Placebo group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
</tr>
<tr>
<td>Kalliomaki et al. (2001)</td>
<td>39.0</td>
<td>1.3</td>
<td>77</td>
</tr>
<tr>
<td>Kaplas et al. (2007)</td>
<td>40.0</td>
<td>0.4</td>
<td>10</td>
</tr>
<tr>
<td>Nishijima et al. (2005)</td>
<td>38.5</td>
<td>1.1</td>
<td>12</td>
</tr>
<tr>
<td>Overall</td>
<td>39.2</td>
<td>0.9</td>
<td>99</td>
</tr>
</tbody>
</table>

SD: standard deviation; n: sample size
3.2 Work performed by the student

Thomas Einarson and I conceptualized this study. Xu Zhu, Xin Chen and I conducted the systematic reviews. Thomas Einarson, Marcio Machado and I conducted the meta-analysis. I drafted the manuscript with contributions on figures and tables by Marcio Machado, Xu Zhu and Xin Chen. Thomas Einarson and Gideon Koren reviewed the final manuscript.

3.3 Statement of significance and impact

To my knowledge, this was the first study to conduct a meta-analysis on the safety of probiotic strains, i.e. *Lactobacillus*, *Bifidobacterium* and *Saccharomyces*, in pregnancy. In addition to applying the evidence-based levels from Chapter 2, this study meta-analyzed the impact on birth weight, gestational age and Caesarian section incidence associated with probiotic use in pregnancy.

Probiotic use in pregnancy may offer therapeutic benefit, where it was shown to decrease the expression of atopic disease in the newborn and was shown to be an effective treatment for BV. The conclusion that certain strains of *Lactobacillus* and *Bifidobacterium* may be of minimal risk during pregnancy and even of therapeutic benefit is of direct impact to the standard of care for expecting mothers. The conclusion that the probiotic strain *Saccharomyces* is not sufficiently researched in pregnancy identifies a probiotic strain that should be avoided in pregnancy until further research confirms its safety.
4 From type 2 diabetes to antioxidant activity, the safety and efficacy of common (*Cinnamomum verum*, *C. zeylanicum*) and cassia (*Cinnamomum aromaticum*) cinnamon bark – A systematic review

Published as a manuscript in the Canadian Journal of Physiology and Pharmacology. The full reference is follows:


4.1 Reference and manuscript

Title: From type 2 diabetes to antioxidant activity, the safety and efficacy of common (*Cinnamomum verum*, *C. zeylanicum*) and cassia (*Cinnamomum aromaticum*) cinnamon bark – A systematic review

Jean-Jacques Dugoua ND PhD (cand.), Dugald Seely BSc ND MSc (cand.), Dan Perri BScPhm MD FRCPC, Kieran Cooley BSc ND MSc (cand.), Taryn Forelli ND BSc, Edward Mills MSc PhD LLM, Gideon Koren MD FABMT FRCPC

**Statement of Conflict:**

Doctors Dugoua, Seely, Cooley, Perri, Mills and Koren have no conflicts of interest to report. Dr. Forelli is the Director of Medical Education for New Chapter, a manufacturer of a cassia and cinnamon natural health product.
ABSTRACT

Introduction: Common (*Cinnamomum verum*, *Cinnamomum zeylanicum*) and cassia (*Cinnamomum aromaticum*) cinnamon have a long history of use as spices and flavoring agents. A number of pharmacological and clinical effects have been observed with their use.

Objective: To systematically review the scientific literature for human pre-clinical and clinical evidence of safety, efficacy and pharmacological activity of common and cassia cinnamon.

Methods: Using the principles of evidence-based practice, we searched 9 electronic databases and compiled data according to the grade of evidence found.

Results: One pre-clinical pharmacological study on antioxidant activity and seven studies on various medical conditions were reported in the scientific literature, including: type 2 diabetes (3), *Helicobacter pylori* infection (1), activation of olfactory cortex of the brain (1), oral candidiasis in HIV (1) and chronic salmonellosis (1).

Discussion: Based on strong scientific evidence from two of three randomized clinical trials reviewed, cassia cinnamon demonstrated a therapeutic effect in reducing fasting blood glucose by 10.3% to 29%; the third clinical trial did not observe this effect. Cassia cinnamon, however, did not have an effect at lowering glycosylated hemoglobin (HbA1c). One randomized clinical trial reported that cassia cinnamon lowered total cholesterol, LDL cholesterol and triglycerides; the other two trials, however, did not observe this effect. There was good scientific evidence that a species of cinnamon was not effective at eradicating *H. pylori* infection. Common cinnamon showed weak to very weak evidence of efficacy in treating oral candidiasis in HIV patients and chronic salmonellosis.

Introduction

Cinnamon bark is widely used as a spice and flavoring agent. There are reports of
cinnamon being imported to Egypt from China as early as 2000 BC. Cinnamon is mentioned in the Bible (Exodus and Proverbs) and in Chinese texts written 4000 years ago \(^1,2\).

Cinnamon is a small evergreen tree, approximately 10-15 m tall, native to Sri Lanka and Southern India. The name cinnamon comes from the Greek *kinnámōmon*, ultimately from the Malaysian and Indonesian *kayu manis*, which means “sweet wood”. Common cinnamon correctly refers to “true cinnamon” or its synonym Ceylon Cinnamon (*Cinnamomum verum, Cinnamomum zeylanicum*) \(^3\). The related species cassia cinnamon (*Cinnamomum aromaticum*) or Chinese cinnamon is sometimes sold labeled as cinnamon \(^3,4\).

Common and cassia cinnamon have been shown to be generally safe when ingested and to have many pharmacological properties, such as antioxidant activity and anti-microbial effects \(^3-7\). Based on pre-clinical and clinical data, common and cassia cinnamon are well known for their pharmacological properties in the treatment of type 2 diabetes \(^8,9\). In rats, both common and cassia cinnamon have been shown to reduce blood glucose following a glucose tolerance test, where cassia was found to be superior to common cinnamon \(^8\). It has even been proposed that the antioxidant properties of common and cassia cinnamon may influence diabetic complications \(^10\). In humans, three randomized controlled trial have been conducted on cassia and its effects on fasting glucose, glycosylated hemoglobin (HbA1c) and lipid profile markers \(^9,11,12\). Often misrepresented in the media and scientific literature, the “cinnamon” bark used in these studies was in fact cassia and not common cinnamon as indicated in their scientific abstracts \(^9,11,12\).

Given the variety of pre-clinical and clinical evidence on common and cassia cinnamon and the fact that people with diabetes are taking natural health products, there is a need to determine safety, efficacy and pharmacological activity. To achieve this objective, we
decided to systematically review the scientific literature for evidence of safety, efficacy and pharmacological activity of common and cassia cinnamon.

**Methodology**

*Search Strategy*

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant pre-clinical and clinical medical literature that provide information as to the safety, efficacy and pharmacology of common and cassia cinnamon. Our strategy employed systematic searches of the following databases from inception to August 2006:

- MedLine (1966-)
- Old Medline (1950-65)
- Cumulative Index to Nursing & Allied Health Literature (CINAHL) (1982-)
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- DARE
- Allied and Complementary Medicine (AMED) (1985-)
- EMBASE (1980-)
- AltHealthWatch

To ensure that reports, trials and other key areas of evidence were not overlooked, the following additional databases were consulted: Complete German Commission E
Monographs by the American Botanical Council, Natural Database and Natural Standard. In addition, we conducted hand searches of all relevant review papers as well as the reference lists of original research publications.

The MeSH terms used for searching included: “cassia”, “cinnamon” and “cinnamomum”. Studies where common and/or cassia cinnamon were not studied on their own, i.e. combination products such as Traditional Chinese medicine patents, were excluded. Given the limited amount of evidence on natural health products in the scientific literature, the search strategy employed for evaluating therapeutic efficacy was designed to capture all human pre-clinical and clinical studies. In order to properly evaluate toxicology, adverse effects and pharmacology, animal and in vitro studies were also included in our search strategy.

Data extraction

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then extracted and compiled in our final report. For evaluation of therapeutic efficacy, each study was rated and assigned a grade of evidence as outlined in Table 1. Special consideration was given for safety during pregnancy and lactation and this is emphasized through the additional assignments on evidence level for harm as outlined in Table 2. The evidence grades used are standardized and described further in previous publications

Results

Therapeutic efficacy

As part of our search strategy on the therapeutic efficacy of common and cassia cinnamon, we identified eight studies involving humans. One pre-clinical
pharmacological study on antioxidant activity and seven studies on various medical conditions were reported in the scientific literature, including: type 2 diabetes (3), Helicobacter pylori infection (1), activation of the olfactory cortex of the brain (1), oral candidiasis in HIV (1) and chronic salmonellosis (1). These studies are discussed in further detail below and summarized in Table 3.

Type 2 diabetes

Mang et al. (2006) (Grade B1) conducted a randomized controlled trial (n=79) of type 2 diabetics where they observed a significantly higher reduction in fasting glucose in the group taking cassia cinnamon (10.3%) versus the placebo group (3.4%) 11. Patients received an aqueous cassia extract corresponding to 3g of cassia cinnamon powder per day or placebo for 4 months. No significant difference was observed in glycosylated hemoglobin A1c (HbA1c), total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triacylglycerol concentrations.

Khan et al. (2003) (Grade B1) conducted a randomized controlled trial (n=60) where they demonstrated that patients randomized to the cassia intervention experienced statistically and clinically significant improvements in blood glucose control and reductions in established cardiovascular risk factor biomarkers 17. This study demonstrated that intake of 1g, 3g or 6g of cassia cinnamon per day reduced serum glucose, triglycerides (TG), LDL-C and Total-C in people with type 2 diabetes. After 40 days of treatment with cassia cinnamon, doses of 1g, 3g and 6g reduced fasting serum glucose by 18-29%, reduced TG by 23-30%, reduced LDL-C by 7-27% and reduced Total-C by 12-26%. No significant changes were noted in the placebo group. The fasting glucose values at baseline where quite high (11.4-16.7 mmol/L) and unfortunately, HbA1c values were not investigated.
Vanschoonbeek et al. (2006) (Grade B2) conducted a small randomized controlled trial (n=25) of postmenopausal patients with type 2 diabetes where they found that supplementation with 1.5g/day (500 mg TID) of cassia cinnamon over 6 weeks did not significantly improve fasting glucose, plasma insulin, Total-C and LDL-C in comparison to the control group. A reduction of HbA1c, HDL-C and TG values following cassia administration was not observed; rather the trend of these measurements was either unchanged or very slightly increased after 6 weeks. Although the methodological quality of this study was good overall, the trial was underpowered to detect a difference in outcomes assessed. It is of note that the dosage used was 50% higher than the lowest dose by Khan et al. (2003) and should, in theory, have been sufficient to demonstrate a therapeutic effect.

*Helicobacter pylori* infection

Nir et al. (2000) (Grade B2) conducted a small randomized controlled pilot study (n=23) of human patients infected with *Helicobacter pylori* (*H. pylori*) where cinnamon extract was shown to be ineffective in eradicating *H. pylori*. Subjects were randomized in a ratio of 2:1 (study:control) to receive 40 mg of an alcoholic cinnamon extract twice daily for 4 weeks or placebo. The amount of *H. pylori* colonization was measured by the $^{13}$C urea breath test (UBT) before and after therapy. The mean urea breath test counts in the treatment and control groups before and after therapy were 22.1 and 23.9 versus 24.4 and 25.9, respectively. Although the authors discussed the trend in their data, statistical significance was not achieved. Seven patients were excluded from the final analysis due to antibiotic use, poor compliance or negligible UBT at baseline. Given the small sample and number of data points excluded from final analysis, the authors may have underpowered this study; also, they did not report if they used intention-to-treat analysis. The cinnamon extract was well tolerated and side effects were minimal. The researchers did not specify which cinnamon species, i.e. cassia or common, was administered.
Activation of the olfactory cortex of the brain

Gonzalez et al. (2006) (Grade C) conducted an observational study on 23 human subjects to determine the effect of abstract linking of linguistic and odour information in the brain using functional magnetic resonance imaging (fMRI)\textsuperscript{19}. Odour-related terms, such as reading the word “cinnamon”, elicited activation in the primary olfactory cortex, which include the piriform cortex and the amygdala.

Oral candidiasis in HIV

Quale et al. (1996) reported a case series of five patients with HIV infection and oral candidiasis that received a commercially available common cinnamon preparation \textit{(Cinnamomum zeylanicum)} for one week\textsuperscript{20}. After one week, three of the five patients demonstrated improvements of their oral candidiasis.

Chronic Salmonellosis

A case (Grade E) was reported of an infant chronic carrier of \textit{Salmonella enteritidis} that improved following the consumption of ground cinnamon bark \textit{(Cinnamomum zeylanicum)} mixed with fruit 3-4 times daily for one month\textsuperscript{21}. The infant contracted salmonellosis from his mother where he became a chronic carrier, indicated by repeated positive stool tests for \textit{S. enteritidis}. One month after consumption of cinnamon bark, stool culture results showed no growth of pathogens. The stool tests remained negative after testing at both two and three month follow-ups. Cinnamon has demonstrated antimicrobial effects in \textit{in vitro} studies, lending support to this clinical observation\textsuperscript{22}. 
Pharmacological study of antioxidant status

Ranjbar et al. (2006) (Grade B2) conducted a comparative cross-sectional pharmacological study on 54 subjects. Individuals consuming cinnamon tea had increased total serum antioxidant status, increased thiols and decreased lipid peroxidation when compared with controls and individuals consuming regular tea. Subjects were randomly divided into three groups: water (control), regular tea, or common cinnamon (Cinnamomum zeylanicum) tea and were instructed to consume the beverages for 2 weeks. Blood samples were obtained at baseline and after two weeks and analyzed for lipid peroxidation levels, total antioxidant power and total thiol groups.

Toxicology and adverse effects

A randomized controlled trial (n=60) of cassia cinnamon demonstrated that intake of up to 6g daily over 40 days did not have any significant adverse effects. Two other trials (n=25 and n=79) of cassia cinnamon dosed at 1.5g/day over 6 weeks and 3g/day over 4 months, respectively, did not report any significant adverse effects. The remaining human studies identified in the previous section did not report any clinically significant adverse effects.

Two textbooks on herbal medicines reported that cinnamon is safe when used in medicinal amounts, but may be of concern when used in excessive amounts or in the long term. One of these texts reported that cinnamaldehyde consumption should not exceed 700 mcg/kg. A case was reported where a child ingested 60 ml of cinnamon oil had serious side effects, including vomiting, diarrhea, dizziness and loss of consciousness.

According to the US Food and Drug Administration (FDA), Cinnamomum sp., including common and cassia cinnamon, are considered as Generally Recognized As Safe (GRAS)
when used in amounts commonly found in food. The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) Adverse Reaction Database by Health Canada was searched from January 1965 to August 2006 and revealed no entries for common or cassia cinnamon.

Low-level evidence from case reports and case series indicate that common and cassia cinnamon may be of concern in excessive amounts. The likely source of these adverse effects may be due to the volatile oil content of common and cassia cinnamon that may irritate skin and mucous membranes. The most common adverse effects reported with common and cassia cinnamon were related to contact irritation or allergic reaction with skin or mucus membranes. Examples include:

- contact dermatitis
- stomatitis
- oral lichen planus
- oral leukoplakia
- mouth burning syndrome
- sunscreen dermatitis
- urticaria
- perioral dermatitis
- oral erythema multiforme-like sensitivity reaction

Less frequent but more severe adverse effects observed in case reports include:
• A case of a 24-year-old woman who developed squamous cell carcinoma of the tongue following persistent and prolonged exposure to cinnamon-flavored chewing gum. Cinnamon gum-chewing was discontinued by the patient and the lesion was surgically removed.

• A case of an 11-year-old boy who presented at a pediatrics clinic with a 10 by 12 cm second-degree burn on his posterior thigh. The blistered area was surrounded by a 3 to 4 cm first-degree burn. The injury was the result of a cinnamon oil spill from a broken vial in his rear pants pocket. The area had remained unwashed for 48 hours, and smelled strongly of cinnamon.

• A series of thirty-two cases of cinnamon oil abuse were reported within a 5-month period at the Pittsburgh Poison Center (PPC). All cases involved males aged 11-16 years. Sucking on toothpicks or fingers, which had been dipped in cinnamon oil was the primary method of abuse. A rush or sensation of warmth, facial flushing and oral burning were the experiences reported by the users. Some children complained of nausea or abdominal pain but no systemic effects were reported.

• A clinical trial reported that topical administration of a herbal preparation SS-cream containing common cinnamon on the glans penis was generally well tolerated, but may cause sporadic erectile dysfunction, excessively delayed ejaculation, mild pain and local irritation and burning.

• A patient with orofacial granulomatosis was found to improve following a cinnamon- and benzoate-free diet.

• Asthma has been reported as a common condition in workers at cinnamon plantations.

Safety pertaining to pregnancy and lactation

There were no reports in the scientific literature of common or cassia cinnamon being safe or harmful during pregnancy and lactation. Since common and cassia cinnamon are
considered as GRAS when used in amounts commonly found in food, it is presumed that food amounts consumed during pregnancy and lactation would also be safe. However, there is no clinical, animal or in vitro evidence to support this evaluation that common and cassia cinnamon are safe in food amounts during pregnancy and lactation.

With respect to therapeutic doses, the safety of cassia cinnamon in pregnancy and lactation is unknown. Common cinnamon is reported as unsafe for use during pregnancy and lactation in two textbooks and “unknown safety” when used during lactation. It is unclear if this warning is an expert opinion based on the absence of reliable scientific evidence and perhaps would be better interpreted and cited as “unknown”.

**Drug interactions**

Although theoretical, the anti-diabetic effect of common and cassia cinnamon may have an additive effect with anti-diabetic medication and insulin. Patients taking anti-diabetic medication or insulin should be monitored by their health care provider when taking common or cassia cinnamon.

**Pharmacology**

Both bark and flower can be used medicinally, however, the bark is more commonly used. Levels of the active constituents will vary depending on the method used in the extraction process. Extensive gas chromatography analysis of cinnamon leaf, stem bark, and root bark oils indicated a total of 72 compounds in varying proportions. Common and cassia cinnamon (Cinnamomum verum and C. aromaticum) contain volatile oils (1–4%) such as cinnamaldehyde (60–80%, 1400-30000 ppm), eugenol (up to 10%) and trans-cinnamic acid (5–10%); phenolic compounds (4–10%) such as condensed tannins, catechins, and proanthocyanidins; monoterpenes and sesquiterpenes (pinene); calcium-
monoterpenes oxalate; gum; mucilage; resin, starch, sugars and traces of coumarin. Antioxidant

The polyphenolic polymers found in *Cinnamomum verum* and *C. aromaticum* have antioxidant activity and have been shown to reduce oxidative stress in a dose dependant manner through inhibition of 5-lipoxygenase enzyme.

Anti-diabetic

Methylhydroxychalcone polymer (MHCP) in common and cassia cinnamon was found to be an effective mimetic of insulin. MHCP demonstrated *in vitro* activation of glycogen synthase and inhibition of glycogen synthase kinase-3beta as well as insulin receptor phosphorylation homologous to the effects of insulin in 3T3-L1 adipocytes. *In vivo* studies show an increase in insulin-stimulated IR-beta and the IRS-1 tyrosine phosphorylation treated with cassia cinnamon. Cinnamon acts as a synergetic agonist with insulin *in vivo* to decrease blood glucose levels following a glucose tolerance test and in chronically high fructose diets.

Neurological

A natural medicine compendium reported that cinnamaldehyde is a central nervous system (CNS) stimulant in high doses, a CNS sedative in low doses, increases peripheral blood flow, slows heart rate, reduces blood pressure and has antipyretic and hypothermic effects. Common cinnamon bark reduces the amplitude of penile somatosensory-evoked potentials in a mechanism that is not clearly understood, but may be useful in the treatment of premature ejaculation.
Antimicrobial

The essential oil has demonstrated strong antibacterial and antifungal activities in vitro. Antifungal, antiviral, bactericidal and larvicidal actions have been reported for the volatile oil. Its constituents eugenol, eugenol acetate and methyl eugenol have been reported to enhance trypsin activity in vitro\(^ {54}\). Cinnamaldehyde has broad spectrum gram positive and gram negative antibacterial activity where it was shown to inhibit the growth of *Clostridium perfringens*, *Bacteroides fragilis*, *Bifidobacterium bifidum*,\(^ {61}\) *Staphylococcus aureus*, *Listeria monocytogenes*, *E. coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Salmonella typhymurium*\(^ {62}\) as well as broad spectrum vaginal microflora\(^ {63}\). One mechanism that has been explored for this antibacterial activity is that cinnamaldehyde destroys the cytoplasmic membrane of both gram-positive and gram-negative bacteria and induces depletion of the intracellular ATP concentration\(^ {64}\).

Cinnamaldehyde has also been shown to inhibit growth of fungi including yeasts (four species of Candida: *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*), filamentous molds, (three *Aspergillus* sp. and one *Fusarium* sp.) and dermatophytes, (Microsporum gypseum, *Trichophyton rubrum* and *T. mentagrophytes*)\(^ {62}\) as well as eggs and adult females of human head louse *Pediculus humanus capitis*\(^ {65}\). Aqueous and alcohol extracts of cinnamon have demonstrated antibacterial effects against *Helicobacter pylori*\(^ {66, 67}\).

Immunomodulatory and anti-neoplastic

Cinnamaldehyde was shown to inhibit lymphocyte proliferation and modulate T-cell differentiation\(^ {68}\). Cinnamaldehyde has anti-tumour activity where it was shown in vitro to be cytotoxic to human solid tumor cells\(^ {69}\), cancer cell lines\(^ {70}\) and a modulator of the
phosphorylation signal pathways that block cellular proliferation at the G2/M phase of the cell cycle.\textsuperscript{71}

\textit{Gastrointestinal}

Cinnamon bark contains tannins which due to their astringent properties likely account for common and cassia cinnamon’s anti-diarrheal effect.\textsuperscript{24}

\textit{Non-mutagenic}

An \textit{in vitro} study using rec assays with \textit{Bacillus subtilis} strains demonstrated that the ethanol extract of common cinnamon (\textit{C. zeylanicum}) was non-mutagenic.\textsuperscript{72} The petroleum ether and chloroform extracts, however, were shown to be mutagenic, thereby suggesting that the mutagenic substance(s) in cinnamon can be extracted by a non-polar solvent (petroleum ether) or a semi-polar solvent (chloroform).\textsuperscript{72}

\textbf{Discussion}

According to the World Health Organization (WHO), approximately 150 million people have type 2 diabetes worldwide, and this number may well double by the year 2025.\textsuperscript{73} Diabetes is a growing health concern and thus there is a need for effective control and management of this disease. Another growing health concern is metabolic syndrome, which is a cluster of conditions (abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance/glucose intolerance, prothrombic state and pro-inflammatory state) that increase the risk for heart disease, stroke and diabetes. According to a cross-sectional survey, the incidence of metabolic syndrome in the United states is 21.8\%.\textsuperscript{74}
Common and cassia cinnamon have been investigated in animal studies for their anti-diabetic properties. Cassia cinnamon, however, has been the subject of three clinical trials while common cinnamon remains unstudied in humans. The three trials on cassia cinnamon ranged from “strong” to “good” with respect to their grade of evidence. The Khan et al. (2003) trial reported the largest benefit of cassia cinnamon in lowering fasting glucose and lipid profile markers. Though the Mang et al. (2006) trial also observed a significant decrease in fasting glucose, the magnitude of the effect was far less dramatic; no significant change was observed in lipid profile markers nor HbA1c following cassia cinnamon intake. The third trial, by Vanschoonbeek et al. (2006), did not observe a significant change in blood sugar or lipid profile markers but this may have been due to the small sample size involved.

The principal criticism of the Khan et al. (2003) study was that baseline fasting glucose values were quite high (11.4-16.7 mmol/L) in comparison to the other two trials. This could be indicative of cassia cinnamon being more effective in reducing fasting glucose levels in uncontrolled diabetics versus controlled diabetics. Mang et al. (2006) reported that the decrease in fasting plasma glucose correlated significantly with baseline concentrations, indicating that subjects with a higher initial plasma glucose level may benefit more from cassia cinnamon intake; thereby supporting the hypothesis that poorly controlled diabetics may benefit more from cassia cinnamon intake. Another possible explanation is that the elevated baseline fasting glucose values in the Khan et al. (2003) trial could be representative of poor blood sugar control in Pakistani diabetics where diabetic treatments (medications, dosing, dietary and exercise recommendations) may vary in comparison to Western diabetics. Fasting glucose levels as high as those observed in the Pakistani diabetics are unusual in Western diabetics due perhaps to a more rapid treatment protocol being instituted. Lastly, Vanschoonbeek et al. (2006), suggested that perhaps their results differ due to the inclusion of only women in their study. Given that the other 2 trials contained women, it is unclear if this would have had any real bearing on the results.
The dosing is likely not an explanation of the observed difference between the three trials as the Khan et al. (2003) trial reported a measurable effect with cassia cinnamon administered between 1g to 6g daily while the two other trials were well within that dosing range, i.e. 1.5g and 3g. The quality of cassia cinnamon could also be a consideration as the products used may have contained different amounts of methylhydroxychalcone polymer (MHCP), which is considered to be the active insulin-mimetic ingredient in common and cassia cinnamon. Mang et al. (2006) reported that each cassia cinnamon capsule contained 112 mg of the aqueous cassia cinnamon extract TC112 (corresponding to 1 g of cinnamon), as prepared by Finzelberg (Andernach, Germany) and obtained from Truw Arzneimittel Vertriebs GmbH (Diabetruw®, Gütersloh, Germany). Khan et al. (2003) described their cassia cinnamon product as “Cinnamomum cassia” as certified by the Office of the Director, Research and Development/Non-Timber Forest Products, NWFP Forest Department, Peshawar, Pakistan and manufactured by Mehran Traders Pharmaceutical Suppliers, Peshawar, Pakistan. Vanschoonbeek et al. (2006), however, provided a far less detailed description of their cassia cinnamon product where they describe their product as “Cinnamomum cassia” prepared by a local pharmacy. Despite relatively good to very poor quality assurance reporting, none of the trials provided detailed chemical analysis of the constituents in their cassia cinnamon intervention. For future study, researchers should select a cassia cinnamon product that is well characterized chemically and provide, at a minimum, the following information: assurance of botanical identity, source of raw material, processing steps, existence of voucher specimens of raw materials as well as saved specimens for future reference.

Although there is strong to good evidence on the efficacy of cassia cinnamon in lowering fasting blood glucose, none of the clinical trials have been able to demonstrate that cassia cinnamon has an effect at reducing HbA1c. Since glucose stays attached to hemoglobin for the life of the red blood cell (normally about 120 days), the level of HbA1c reflects
the average blood glucose levels over the past 3 months. The HbA1c data from the Vanschoonbeek et al. (2006) study is not clinically relevant as the study was conducted over 6 weeks from baseline to endpoint. In the Mang et al. (2006) study, HbA1c was not significantly reduced after 4 months of treatment with cassia cinnamon, nor was there a decreasing trend in HbA1c data from baseline to post-treatment. Before cassia or common cinnamon can be recommended as a natural alternative to pharmacological agents in treating type 2 diabetes, effectiveness in lowering HbA1c needs to be demonstrated. When conducting future randomized controlled clinical trials, the study length should be extended to perhaps 6 months or maybe even a year in order to truly evaluate a change, if any, in HbA1c.

Common and cassia cinnamon have been shown to have antioxidant activity in vitro. Common cinnamon appears to have antioxidant activity in humans where individuals consuming cinnamon tea had increased total antioxidant power, increased thiols and decreased lipid peroxidation when compared with controls and individuals consuming regular tea.\textsuperscript{23} It has been suggested that the antioxidant properties of common and cassia cinnamon may contribute to its anti-diabetic effects, as there are a small number of clinical studies where antioxidants, such as vitamin E, buckwheat herb, Ruscus extract and troxerutinaos, were shown to reduce or slow the progression of diabetic complications.\textsuperscript{10,75-77} This is perhaps an area of future clinical research for common and cassia cinnamon.

Although cinnamon was shown to have antibacterial activity against \textit{H. pylori} in vitro, a small pilot study, however, demonstrated that an alcoholic cinnamon extract over 4 weeks did not eradicate \textit{H. pylori}. Based on weak scientific evidence from a case series, common cinnamon was shown to be beneficial in treating oral candidiasis in HIV patients. One case of salmonellosis was reported where a chronic carrier of \textit{Salmonella enteritidis} was resolved following the ingestion of ground common cinnamon bark. At this time, however, the clinical data does not indicate that cassia, common or any other
species of cinnamon should be recommended as a natural alternative for treating *H. pylori* infections, oral candidiasis in HIV patients or salmonellosis. Although these studies are promising, further clinical research on common and cassia cinnamon is needed to strengthen the evidence grade for these therapeutic indications.

With respect to safety, common and cassia cinnamon appear to be generally well tolerated. The most common adverse effects are related to contact irritation or allergic reaction. There is one case wherein squamous cell carcinoma following long-term cinnamon gum-chewing was reported. Although cinnamon has not been specifically implicated as a carcinogenic agent as its ethanolic extract was shown to be non-mutagenic, caustic chemical irritants acting through cytotoxic mechanisms can have carcinogenic activity when excessive doses exceed threshold levels. Of some concern is the case where a first and second burn was convincingly linked to cinnamon oil exposure. There were a number of cases of cinnamon oil abuse reported in adolescent males (11-16 years) where some complained of nausea or abdominal pain, but no systemic effects were observed. With respect to pregnancy and lactation, the safety of cassia and cinnamon at therapeutic levels remains unknown but is believed to be safe when taken in amounts found in food. When designing future clinical studies, researchers should make note of common and cassia cinnamon’s mucus membrane irritating effects and use products that are encapsulated versus liquid extracts.

Lastly, reading the word “cinnamon” appears to activate the olfactory cortex in the brain as determined by fMRI. Given that the inclusion criteria of our search strategy included all pre-clinical and clinical human studies, this study was presented in this systematic review. Although interesting results, this finding was not discussed in detail as our systematic review is primarily concerned with the pre-clinical and clinical effects of common and cassia cinnamon.
Acknowledgements

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Sick Kids Hospital

Sick Kids Foundation

McMaster University

New Chapter

References


20. Quale JM, Landman D, Zaman MM, Burney S, Sathe SS. In vitro activity of Cinnamomum zeylanicum against azole resistant and sensitive Candida species


30. Leifer W. Contact dermatitis due to cinnamon; recurrence of dermatitis following oral administration of cinnamon oil. *AMA Arch Derm Syphilol.* Jul 1951;64(1):52-55.


Table 1. Levels of evidence for efficacy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><strong>Very Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.</td>
</tr>
<tr>
<td>B1</td>
<td><strong>Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more properly conducted randomized controlled trials (RCTs).</td>
</tr>
<tr>
<td>B2</td>
<td><strong>Good scientific evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.</td>
</tr>
<tr>
<td>C</td>
<td><strong>Fair Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more cohort studies OR outcome studies OR case control studies.</td>
</tr>
<tr>
<td>D</td>
<td><strong>Weak Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case series.</td>
</tr>
<tr>
<td>E</td>
<td><strong>INDIRECT and/or Clinical evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case reports OR expert opinion OR laboratory studies.</td>
</tr>
<tr>
<td>F</td>
<td><strong>Historical or traditional evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.</td>
</tr>
</tbody>
</table>
Table 2. Levels of evidence for harm

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| 1a    | **Very Strong scientific evidence**  
Statistically significant evidence from one or more systematic reviews or RCTs. |
| 1b    | **Strong Scientific evidence**  
Statistically significant evidence from one or more outcome studies OR cohort studies OR case control studies. |
| 1c    | **Good Scientific evidence**  
Evidence from one or more case series. |
| 2     | **Fair Scientific evidence**  
Evidence based on case reports. |
| 3     | **In vitro scientific evidence**  
Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells. |
| 4     | **INDIRECT evidence**  
Evidence based on scientific theory OR expert opinion. |
| 5     | **Unknown**  
No available information. |
Table 3: Cassia and cinnamon evidence table

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author (year)</th>
<th>n</th>
<th>Results</th>
<th>Statistically significant</th>
<th>Type of cinnamon</th>
<th>Dosage (daily)</th>
<th>Evidenc e grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>Randomized controlled trial</td>
<td>Mang et al. (2006)</td>
<td>79</td>
<td>Reduced fasting glucose by 10.3%. No effect on HbA1c and lipid profile</td>
<td>Yes</td>
<td>Cassia</td>
<td>3 g</td>
<td>B1</td>
<td>Strong scientific evidence. Moderate effect on fasting glucose.</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Randomized controlled trial</td>
<td>Khan et al. (2003)</td>
<td>60</td>
<td>Reduced fasting serum glucose by 18-29%, reduced triglyceride by 23-30%, reduced LDL cholesterol by 7-27% and reduced total cholesterol by 12-26%</td>
<td>Yes</td>
<td>Cassia</td>
<td>1, 3 or 6 g</td>
<td>B1</td>
<td>Strong scientific evidence. Strong effect of fasting glucose and lipid profile markers (TG, LDL-C and Total-C).</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Randomized controlled trial</td>
<td>Vanschoonbeek et al. (2006)</td>
<td>25</td>
<td>No change in fasting glucose, insulin, HbA1c, oral glucose tolerance or lipid profile</td>
<td>No</td>
<td>Cassia</td>
<td>1.5 g</td>
<td>B2</td>
<td>Good scientific evidence. No effect. Small sample size.</td>
</tr>
<tr>
<td>Helicobacter pylori infection</td>
<td>Randomized controlled trial</td>
<td>Nir et al. (2000)</td>
<td>23</td>
<td>Not effective at eradicating <em>H pylori</em></td>
<td>No</td>
<td>Cassia or cinnamon – not specified</td>
<td>80 mg</td>
<td>B2</td>
<td>Good scientific evidence. No effect. Small sample size. Study does not specify whether cassia or cinnamon was the intervention</td>
</tr>
</tbody>
</table>
Table 3: Cassia and cinnamon evidence table (cont.)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author (year)</th>
<th>n</th>
<th>Results</th>
<th>Statistically significant</th>
<th>Type of cinnamon</th>
<th>Dosage (daily)</th>
<th>Evidenc e grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of olfactory cortex of the brain</td>
<td>Observational study</td>
<td>Gonzalez et al. (2006)</td>
<td>23</td>
<td>Reading the word “cinnamon” elicited activation in the primary olfactory cortex</td>
<td>No</td>
<td>“cinnamon” as a word</td>
<td>N/A</td>
<td>C</td>
<td>Fair scientific evidence. Observational study using the word “cinnamon”</td>
</tr>
<tr>
<td>Oral candidiasis in HIV</td>
<td>Case series</td>
<td>Quale et al. (1996)</td>
<td>5</td>
<td>Improvement in oral candidiasis</td>
<td>No</td>
<td>Common</td>
<td>N/A</td>
<td>D</td>
<td>Weak scientific evidence. No placebo. Small sample size. Quantity of dosage not described.</td>
</tr>
</tbody>
</table>
4.2 Work performed by the student

I was responsible for the inception of this systematic review. I conducted the review and analysis of the clinical studies extracted. I wrote the vast majority of the manuscript, with contributions on adverse effects by Kieran Cooley. Gideon Koren, Dan Perri, Dugald Seely and Taryn Forelli provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

4.3 Statement of significance and impact

This manuscript was the first systematic review to explore the scientific data on both common and cassia cinnamon; in the past, cassia cinnamon has been the main focus. The systematic review reported methodological flaws in two previously published clinical trials where HA1c data were reported that were not applicable (HA1c values collected <90 days in between measurements). Unfortunately, meta-analyses since have included these invalid HA1c data in their analyses. Although the evidence is preliminary, common and cassia cinnamon could be investigated as a NHP alternative to anti-diabetic drugs for women with gestational diabetes.
5 Safety and efficacy of St. John’s wort *(Hypericum)* during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


5.1 Reference and manuscript

Title: Safety and efficacy of St. John’s wort *(Hypericum)* during pregnancy and lactation

Jean-Jacques Dugoua ND BSc (Hons.)

Edward Mills DPH MSc

Daniel Perri MD BscPharm FRCP(C)

Gideon Koren MD

Abstract

**Background:** There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for common herbs used during pregnancy and lactation.
Objectives: To systematically review the literature for evidence on the use, safety, and pharmacology of St. John’s wort focusing on issues pertaining to pregnancy and lactation.

Methods: We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results: We found varying levels of scientific evidence on efficacy of use for different conditions, low-level evidence of harm during pregnancy and strong evidence of side effects during lactation.

Conclusions: St. John’s wort shows strong scientific evidence of being an effective aid in combating mild to moderate depression and low-level evidence for other conditions. Caution is warranted with the use of St John’s wort during pregnancy and lactation. During pregnancy, a case study and some animal studies reported no side effects, while other animal studies reported lower birth weights with use of St John’s wort. Strong scientific evidence shows that St. John’s wort consumption during lactation does not affect maternal milk production nor affect infant weight, but may cause colic, drowsiness or lethargy.

Keywords: St. John’s wort, Hypericum perforatum, pregnancy, lactation, breastfeeding, systematic review

Introduction

Hypericum perforatum is an aromatic perennial herb that produces a star-shaped golden yellow flower. It is native to Europe, Northern Africa, and Western Asia but can be found growing throughout the world. The common name of the plant likely originates from “Saint John’s Day”, June 24, around which time the plants typically bloom. Hippocrates and Galen described the use of Hypericum perforatum as a treatment against demonic possession.
Its Latin name is derived from “hyper” meaning “over” and “eikon” meaning “apparition”: a clear reference to its historical use in treating demonic possession. Its use in treating depression dates back to the time of Swiss physician Paracelsus (ca. 1493-1541) but many authorities believe that the ancient Greeks used it for treating psychiatric disease that they labeled as demonic possession. Throughout the ages it has been used for digestive disorders, worms, wound healing, fevers, and snakebites. It was very popular until the advent of synthetic medicines. It was “rediscovered” in the late 1970s and early 1980s by German physicians who eventually had it approved as a prescription medication for depression by Commission E in 1984. It soon outsold every other anti-depressant drug in Germany and remains covered on the national health care plan. Even today, many German physicians save synthetic antidepressants until a treatment with St. John’s wort has failed.

Mood disorders are among the most common health problems in women and it is diagnosed twice as often in women than men. Almost 10% of women experience depression during pregnancy and patients with a history of depression are at risk for puerperal worsening of mood. A clinical dilemma often results during pregnancy and lactation due to the wish to avoid fetal and neonatal exposure to potential toxins while limiting the risks of untreated psychiatric disorders like depression. Some patients may turn to “natural” medicines such as St. John’s wort that they may perceive to be a safer alternative. However, data regarding the use of natural products in pregnancy and lactation is scarce. The Organization of Teratology Information Services (OTIS) reports in their statement on St. John’s wort that “the limited data limits our ability to draw conclusions about whether there is an increased risk for birth defects or other problems associated with use of St. John’s wort during pregnancy.” For this reason, we have undertaken a systematic review of the literature regarding the efficacy and safety of the use of St. John’s wort by pregnant or breastfeeding women.
Synonyms/Common Names/Related Substances

Amber, amber touch-and-heal, demon chaser, *fuga daemonum*, goatweed, hardhay, hypereikon, hyperici herba, hypericum, Johns wort, klamath weed, millepertuis, Rosin rose, Saint Johns wort, Saint John's wort, Saynt Johannes wort, SJW, St Johns wort, St John's wort, tipton weed

Constituents

Naphthodianthrones: hypericin, pseudohypericin

Flavonoids: quercetin, quercetrin, amentoflavone, hyperin

Phloroglucinols: hyperforin, adhyperforin

Essential oil

Part used

Whole plant

Methods

We searched the following databases from inception to June 2004: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as keywords along with “pregnancy”, “lactation” and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.
Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The grade of evidence for indications was evaluated as displayed in Table 1. We rated evidence of harm as displayed in Table 2.

### Results

#### Indications for use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate depression(^8-12)</td>
<td>A</td>
</tr>
<tr>
<td>Anxiety (with valerian)(^13)</td>
<td>B2</td>
</tr>
<tr>
<td>Acute otitis media (with <em>Verbascum thapsus, Calendula flores</em> and <em>Allium sativum</em>)(^14)</td>
<td>B2</td>
</tr>
<tr>
<td>Obsessive compulsive disorder (OCD)(^15)</td>
<td>C</td>
</tr>
<tr>
<td>Psychological menopause symptoms(^16)</td>
<td>C</td>
</tr>
<tr>
<td>Premenstrual syndrome (PMS)(^17)</td>
<td>C</td>
</tr>
<tr>
<td>Chronic colitis (with <em>Taraxacum officinale, Melissa officinalis, Calendula officinalis</em> and <em>Foeniculum vulgare</em>)(^18)</td>
<td>C</td>
</tr>
<tr>
<td>Seasonal affective disorder (SAD)(^19-21)</td>
<td>C</td>
</tr>
</tbody>
</table>
### Safety of consumption during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal healthy baby(^{22})</td>
<td>2</td>
</tr>
<tr>
<td>Does not affect cognitive development(^{23})</td>
<td>3</td>
</tr>
<tr>
<td>No long-term behavioural deficits(^{24})</td>
<td>3</td>
</tr>
<tr>
<td>Lowers offspring weight(^{24,25})</td>
<td>3</td>
</tr>
<tr>
<td>Does not affect long-term growth and physical maturation(^{26})</td>
<td>3</td>
</tr>
<tr>
<td>Conflicting evidence: Non-mutagenic(^{27}) / Teratogenic(^{28})</td>
<td>3</td>
</tr>
<tr>
<td>Increases uterine tone(^{29})</td>
<td>3</td>
</tr>
<tr>
<td>Emmenagogue(^{30})</td>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant(^{30})</td>
<td>4</td>
</tr>
<tr>
<td>Abortifacient(^{30})</td>
<td>4</td>
</tr>
</tbody>
</table>

A case of a 38-year-old women who started taking St. John’s wort at 24 weeks gestation was reported in a letter to the editor\(^{22}\). The woman’s pregnancy was unremarkable, with the exception of late onset of thrombocytopenia (the author did not attribute this to St. John’s wort)\(^{22}\). The offspring was born healthy, had a normal birth weight, normal APGAR scores and physical examination and laboratory results were normal\(^{22}\). Behavioural assessment at 4 and 23 days was within normal\(^{22}\).

A study on the cognitive impact of prenatal exposure to St. John’s wort in mice for 2 weeks before mating and throughout gestation found that prenatal exposure to a therapeutic dose of St. John’s wort did not have a major impact on certain cognitive tasks in mice offspring\(^{23}\).
A study was conducted where Sprague-Dawley rats were exposed to dietary doses of St. John’s wort 1-25 times the recommended human dose. St. John’s wort had no effect on maternal weight gain or duration of gestation. Offspring body weights were similar to controls, but some treated groups, offspring weighed significantly less than the controls. There were no S. John’s wort-related behavioural alterations on any measure. Whole and regional brain weights of offspring at adulthood indicated no significant effects of St. John’s wort. A behavioural study on mice offspring exposed antenatally to the Saint John's wort found that birth weights of male offspring were less in the Saint John's wort group than in the placebo group. Offspring in both treatment groups showed no long-term statistical differences in early developmental tasks, locomotor activity, and exploratory behavior throughout development. Performances on a depression task and on anxiety tasks revealed no differences between treatment groups.

St. John’s wort was administered to mice in order to determine whether prenatal exposure to the herb affects long-term growth and physical maturation of mouse offspring. Maternal administration of St. John’s wort before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring.

A study on organogenesis found that hypericin induced teratogenic effects in whole rat embryo cultures. A study on mammalian cells, however, showed that a standardized aqueous ethanolic of St. John’s wort did not induce any mutagenic effects.

St. John’s wort was shown to increase uterine tone in animals.
A review article on the potential value of plants as sources of anti-fertility agents reported that St. John’s wort is an abortifacient, emmenagogue and uterine stimulant.\(^{30}\)

A homeopathic preparation of *Hypericum perforatum*, called Hypericum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Although the principles of homeopathy are difficult to apply to evidence-based medicine research, a systematic review determined that homeopathic preparations do not significantly differ from placebo.\(^{31}\)

### Safety of consumption during lactation

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not affect maternal milk production(^{32})</td>
<td>1b</td>
</tr>
<tr>
<td>Does not affect infant weight(^{32})</td>
<td>1b</td>
</tr>
<tr>
<td>May cause colic, drowsiness or lethargy(^{32})</td>
<td>1b</td>
</tr>
<tr>
<td>Crosses into breast milk(^{33})</td>
<td>2</td>
</tr>
</tbody>
</table>

A prospective observational cohort study was conducted on 33 breastfeeding women receiving St. John's wort (Group 1) and for comparison, 101 disease-matched (Group 2) and 33 age- and parity-matched non-disease controls (Group 3).\(^{32}\) In the group receiving St. John’s wort, there were 2 cases of colic, 2 cases of drowsiness and 1 case of lethargy. Specific medical treatment was not required for the infants.\(^{32}\) No significant difference was observed in the frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life.\(^{32}\)
An analysis was performed on four breast-milk samples (fore and hind milk) during an 18-hour period from a mother with post-natal depression who had taken St. John’s wort during pregnancy in order to measure concentration of hypericin and hyperforin\textsuperscript{33}. Only hyperforin was excreted into breast milk at a low level\textsuperscript{33}. No side effects were seen in the mother or infant\textsuperscript{33}.

A homeopathic preparation of \textit{Hypericum perforatum}, called Hypericum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Although the principles of homeopathy are difficult to apply to evidence-based medicine research, a systematic review determined that homeopathic preparations do not significantly differ from placebo\textsuperscript{31}.

\textbf{Toxicity}

St. John’s wort may cause delayed hypersensitivity photodermatitis\textsuperscript{34-36}. Hypericin is believed to be the photosensitizing agent present in St. John’s wort\textsuperscript{37,38}.

\textbf{Pharmacology}

St. John's wort effects on serotonin may be primarily responsible for its antidepressant activity\textsuperscript{39}. Extracts of St. John's wort inhibit the reuptake of serotonin, norepinephrine, and dopamine in vitro\textsuperscript{39-41}. Hyperforin and adhyperforin were shown to modulate the effects of serotonin, dopamine, and noradrenaline, and to act as serotonergic 5-HT3 and 5-HT4 receptor antagonists\textsuperscript{41-44}. Hypericin inhibits \textit{in vitro} almost irreversibly both type A and B monoamine oxidase (MAO) in rat brain mitochondria\textsuperscript{45}. 

In human and animal cancer cells, hyperforin inhibited tumour cell growth by induction of apoptosis\textsuperscript{46}. Topical application of St John's wort inhibits the proliferation of T lymphocytes in inflammatory skin disorders\textsuperscript{47}.

St. John's wort induces some of the cytochrome P450 (CYP) enzymes and may interfere with drug metabolism\textsuperscript{48}. St. John’s wort has antibacterial activity\textsuperscript{49}.

**Drug interactions**

St. John’s wort has displayed consistent pharmacokinetic drug interactions in clinical trials resulting in reduced systemic exposure to many conventional drugs. The following drugs should be noted for potential interactions:

- 5-HT\(_1\) agonists\textsuperscript{50, 51}
- Alprozolam\textsuperscript{52}
- Aminolaevulinic acid\textsuperscript{53}
- Amitriptyline\textsuperscript{54-56}
- Analgesics with serotonergic activity\textsuperscript{30-41, 51}
- Antidepressants\textsuperscript{51, 57-59}
- Barbituates\textsuperscript{60}
- Carbamazepine\textsuperscript{61}
- Cyclosporine\textsuperscript{50, 55, 56, 62-72}
- Digoxin\textsuperscript{50, 56, 73-75}
- Dextromethorphan\textsuperscript{39-41, 51}
- Fenfluramine\textsuperscript{59}
- Fexofenadine\textsuperscript{76}
- Irinotecan\textsuperscript{77, 78}
- Monoamine Oxidase Inhibitors (MAOIs)\textsuperscript{41, 43}
- Mycophenolate mofetil\textsuperscript{79}
- Narcotics\textsuperscript{60, 80}
- Nelazodone\textsuperscript{81}
- Nonnucleoside Reverse Transcriptase Inhibitors\textsuperscript{55, 82, 83}
Nortriptyline$^{54, 56}$

Oral contraceptives$^{60, 84-86}$

Paroxetine$^{51, 58, 59}$

Phenobarbital$^{50}$

Phenprocoumon$^{50}$

Phenytoin$^{50}$

Photosensitizing drugs$^{57}$

Protease Inhibitors (PIs)$^{50, 56, 82}$

Reserpine$^{60}$

Sertraline$^{81}$

Simvastatin$^{87}$

Tacrolimus$^{79, 88}$

Theophylline$^{50, 56, 89}$

Warfarin$^{50, 84, 90}$

Drugs metabolized by cytochrome P450 enzymes$^{48, 50, 52, 56, 65, 74, 75, 82, 84, 91}$
Discussion

There is strong evidence to support the use of St. John’s wort for mild to moderate cases of depression. There is low-level of evidence that support the use of St. John’s wort, alone or in combination with other medicinal herbs, for the following conditions: anxiety, acute otitis media, obsessive compulsive disorder (OCD), psychological menopause symptoms, premenstrual syndrome (PMS), chronic colitis and seasonal affective disorder (SAD).

Despite fair evidence as to the safety of consumption of St. John’s wort during pregnancy, caution is warranted. One case was reported of the birth of a normal healthy baby following St. John’s wort consumption during pregnancy. A small number of animal studies showed that St. John’s wort 1) does not affect cognitive development, 2) causes no long-term behavioural deficits, and 3) does not affect long-term growth and physical maturation. However, other animal studies report lower birth weight in offsprings when St. John’s wort is consumed during pregnancy and that it may increase uterine tone. There is also conflicting evidence as to the teratogenicity of hypericin, yet non-mutagenic activity of the whole plant.

During lactation, St. John’s wort should be used with caution due to potential side effects of colic, drowsiness and lethargy. Despite strong scientific evidence that St. John’s wort consumption during lactation does not affect maternal milk production nor affect infant weight, a few cases of colic, drowsiness or lethargy were reported with its use. There is also fair evidence that St. John’s wort constituents cross into breast milk.

While traditional and common use has not indicated any substantive risks of taking this herb during pregnancy and lactation, clearly more rigorous and well-controlled research is needed in this area. Clinicians and patients should also be concerned about the potential for interactions that may occur between St. John’s wort and numerous prescription medications. This issue has greater significance when the possibility for increased exposure or toxicity to the developing
fetus might result from altered drug metabolism due to interaction. Patients should also be vigilant about sun exposure as St. John’s wort may cause photodermatitis.

REFERENCES


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<td>In vitro scientific evidence</td>
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5.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed
Mills and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

5.3 Statement of significance and impact

To my knowledge, this is the first systematic review to examine the effect of St. John’s wort in pregnancy and lactation. St. Johns wort is a popular NHP for treating depression. In cases where pregnant women seek alternatives to anti-depressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and others, they are likely to consider St. John’s wort treatment. Examining the safety of St. John’s wort during pregnancy and lactation is clinically relevant.
6 Safety and efficacy of Ginkgo (Ginkgo biloba) during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


6.1 Reference and manuscript

Title: Safety and efficacy of Ginkgo (Ginkgo biloba) during pregnancy and lactation

Jean-Jacques Dugoua ND, BSc (Hons.); Edward Mills DPH, MSc; Daniel Perri MD, BscPharm, FRCP(C); Gideon Koren MD

Abstract

Background: There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for common herbs used during pregnancy and lactation.

Objectives: To systematically review the literature for evidence on the use, safety, and pharmacology of ginkgo focusing on issues pertaining to pregnancy and lactation.

Methods: We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results: We found varying levels of scientific evidence on efficacy of use for different conditions, low-level evidence for harm during pregnancy and unknown safety or harm during lactation.
Conclusions: Ginkgo leaf shows very strong scientific evidence for treating intermittent claudication, dementia (including Alzheimer’s disease), cerebrovascular insufficiency and tinnitus. Ginkgo also shows strong scientific evidence for use in age-associated memory impairment, memory enhancement in healthy individuals, altitude sickness, vertigo and premenstrual syndrome (PMS); and good evidence for use in macular degeneration. There is a valid concern that ginkgo use could prolong bleeding during delivery due to its antiplatelet properties. Patients and clinicians should be aware of past reports of ginkgo products being adulterated with colchicine. The safety of ginkgo during lactation is unknown.

Keywords: Ginkgo, Ginkgo biloba, pregnancy, lactation, breastfeeding, systematic review

Introduction

The ginkgo biloba tree is the world’s oldest living tree – its species can be dated back to over 250 million years. It is believed that they once occurred naturally in Asia, Europe and America but they disappeared from America about 7 million years ago and from Europe about 3 million years ago. It wasn’t until the eighteenth century that ginkgo was cultivated again in Europe and North America. It is a very hearty plant and, in fact, in the spring following the atomic bombing of Hiroshima, an old ginkgo tree was the only flora to resprout. The use of Ginkgo for medicinal uses can be traced back to the oldest Chinese materia medica – about 2800 BC. Traditional Chinese medicine has used the ginkgo leaves for brain disorders, circulatory disorders, respiratory diseases such as asthma, urinary tract disorders, and as an antiparasitic. Modern research on ginkgo and the physiologic effects of its constituents began in Japan in the 1920s with its cardiovascular effects documented as early as 1965, and the first standardized extract available on the market in 1975¹.

Ginkgo leaf extracts are now among the leading prescription medicines in both Germany and France, where they account for 1 and 1.5%, respectively, of total prescription sales. Over the last few years ginkgo has also become the top selling herbal medicine in the United States². It is used to treat mild dementia, peripheral vascular disease, and tinnitus. It is also commonly used as a memory enhancer by healthy patients. Although its popularity in women’s health is for stroke
and dementia in the elderly, it is used by women of childbearing age for memory boosting, asthma, mountain sickness, varicose veins, or sometimes for idiopathic cyclic edema. More recently, it has had a growing popularity in the treatment of sexual dysfunction secondary to the use of selective serotonin reuptake inhibitors. It is also used by young women with connective tissue disorders and, in fact, the World Health Organization has recommended the use of ginkgo in Raynaud’s disease.

Although women of reproductive age use ginkgo for a variety of indications, there is disagreement among scientists, clinicians, herbalists, and consumers with regards to the effectiveness and safety of ginkgo. Furthermore, there is debate regarding the safety of ginkgo during pregnancy or breastfeeding. In this paper we address the issues of efficacy of ginkgo for a variety of indications as well as the safety of gingko use by pregnant or breastfeeding women by reporting the results of a systematic review of the literature on ginkgo biloba’s clinical use.

**Synonyms/Common Names/Related Substances**


**Constituents**

Leaf: Flavonoids (rutin, isorhamnetine, quercetin, kaempferol, proanthocyanidins), terpenoids (ginkgolides A, B, C, M and J, bilobalide), organic acids

Seed: Cyanogenic glycosides, ginkgotoxin

**Parts used**

Leaf, seed
Methods

We searched the following databases from inception to June 2004: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as keywords along with “pregnancy”, “lactation” and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The grade of evidence for indications was evaluated as displayed in Table 1. We rated evidence of harm as displayed in Table 2.
## Results

### Indications for use

#### Leaf

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Intermittent claudication – Peripheral vascular disease^{11-13}</td>
<td>A</td>
</tr>
<tr>
<td>Dementia (Alzheimer’s disease and other)^{8,14,15}</td>
<td>A</td>
</tr>
<tr>
<td>Cerebrovascular insufficiency^{16-18}</td>
<td>A</td>
</tr>
<tr>
<td>Tinnitus^{19,20}</td>
<td>A</td>
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<tr>
<td>Age-associated memory impairment^{21-23}</td>
<td>B1</td>
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<tr>
<td>Memory enhancement in healthy individuals^{24-26}</td>
<td>B1</td>
</tr>
<tr>
<td>Altitude sickness^{27}</td>
<td>B1</td>
</tr>
<tr>
<td>Vertigo^{17}</td>
<td>B1</td>
</tr>
<tr>
<td>Premenstrual syndrome (PMS)^{28}</td>
<td>B1</td>
</tr>
<tr>
<td>Macular degeneration^{29}</td>
<td>B2</td>
</tr>
<tr>
<td>Erectile dysfunction^{30-33}</td>
<td>C</td>
</tr>
<tr>
<td>Antidepressant-induced sexual dysfunction^{34}</td>
<td>C</td>
</tr>
<tr>
<td>Chemotherapy adjunct^{35,36}</td>
<td>C</td>
</tr>
<tr>
<td>Multiple sclerosis^{37}</td>
<td>D</td>
</tr>
<tr>
<td>Light-induced retinal damage^{38}</td>
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**Seed**

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<tr>
<td>Cough, expectorant, asthma, bronchitis⁶</td>
<td>E</td>
</tr>
<tr>
<td>Skin sores and scabies (topical)⁶</td>
<td>E</td>
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**Safety of consumption during pregnancy**

**Leaf**

<table>
<thead>
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<tr>
<td>Unsafe when adulterated with colchicine³⁹</td>
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</tr>
<tr>
<td>Antiplatelet³⁸, ⁴⁰, ⁴¹</td>
<td>3</td>
</tr>
<tr>
<td>Emmenagogue⁴²</td>
<td>4</td>
</tr>
<tr>
<td>Hormonal changes⁴²</td>
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**Roasted seed**

<table>
<thead>
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<td>Possibly safe if taken as food¹⁰</td>
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**Raw Seed**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly unsafe⁹</td>
<td>4</td>
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</tbody>
</table>

A case series reported the presence of colchicine in the placental blood of pregnant women having taken ginkgo³⁹. The source of colchicine was traced back to the consumption of commercially available *Ginkgo biloba* products that contained colchicine³⁹. Given that colchicine is not a common constituent of ginko, the observed finding is most likely due to an adulteration of a ginkgo product by a herb containing colchicine.
The antiplatelet properties of ginkgo leaf may prolong bleeding during delivery.\textsuperscript{38, 40, 41}

A herb toxicology and drug interaction compendium reported that ginkgo leaf is an emmenagogue and can cause hormonal changes.\textsuperscript{42} Ginkgo leaf was not reported in the evidence-based medicine literature as being an emmenagogue or causing hormonal changes, nor was it reported as being contraindicated in pregnancy.

A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during pregnancy.\textsuperscript{10} A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in pregnancy if they are used medicinally.\textsuperscript{9} Roasted and raw ginkgo seed were not reported in the evidence-based medicine literature as being either safe or contraindicated in pregnancy.

**Safety of consumption during lactation**

**Leaf**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Roasted seed**

| Possibly safe if taken as food\textsuperscript{10} | 4 |

**Raw Seed**

| Possibly unsafe\textsuperscript{9} | 4 |
Ginkgo leaf was not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during lactation\textsuperscript{10}. A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in lactation if they are used medicinally\textsuperscript{9}. Roasted and raw ginkgo seed were not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

**Toxicology**

Leaf: Crude extracts of ginkgo leaf may contain ginkgolic acids, which are suspected to have cytotoxic, allergenic, mutagenic and carcinogenic properties\textsuperscript{43,44}. The LD\textsubscript{50} in mice is 7,725mg\textsuperscript{45}.

Seed: Ginkgotoxin, found in ginkgo seed, may cause seizures, loss of consciousness and death\textsuperscript{9,10}.

**Pharmacology**

*Leaf*

Ginkgo increases cerebral and peripheral blood circulation\textsuperscript{46,47}. Ginkgo reduces vascular permeability, causes vascular contraction, improves venous tone, inhibits phosphodiesterase type 4 (PDE4), relaxes vascular smooth muscle via a nitric oxide pathway and improves blood flow to the corpus cavernosum of the penis\textsuperscript{30,46-48}. Ginkgo reduces platelet aggregation by competitively binding platelet activating factor (PAF) and by inhibiting the formation of platelet thromboxane A\textsubscript{2}\textsuperscript{38,40,41,49}.
The ginkgo flavonoids have antioxidant and free radical scavenging properties\textsuperscript{8, 15, 38, 40, 50}. Partially due to its antioxidant activity, ginkgo inhibits the toxicity and cell death induced by beta-amyloid plaques in Alzheimer’s disease\textsuperscript{51}. Ginkgo decreases systolic and diastolic blood pressure, increases fasting plasma insulin and C-peptide, decreases cortisol secretion and decreases the secretion of corticotropic releasing hormone (CRH)\textsuperscript{40, 52, 53}.

Ginkgo may inhibit cytochrome P450 3A4, induce cytochrome P450 3A5 and mildly inhibit cytochrome P450 1A2 and 2D6\textsuperscript{6, 54, 55}.

\textit{Seed}

The cyanogenic glycosides have antibacterial and antifungal effects\textsuperscript{6, 9}.

\textbf{Drug interactions}

\textit{Leaf}

- Anticoagulant/Antiplatelet Drugs\textsuperscript{38, 40, 41}.
- Fluoxetine\textsuperscript{56}.
- Buspirone\textsuperscript{56}.
- St. John’s wort\textsuperscript{56}.
- Melatonin\textsuperscript{56}.
- Insulin\textsuperscript{40}.
- Monoamine oxidase inhibitors (MAOIs)\textsuperscript{57-59}.
- Seizure threshold lowering drugs\textsuperscript{60, 61}.
• Thiazide diuretics\textsuperscript{62}.

• Trazodone\textsuperscript{55}.

• Warfarin\textsuperscript{63}.

• Drugs metabolized by cytochrome P4503A4, P450 3A5, P450 1A2 and P450 2D6 enzymes\textsuperscript{6, 54, 55}.

Discussion

Most of the beneficial therapeutic effects of \textit{Ginkgo biloba} appear to be derived from the leaf. There is very strong evidence for the therapeutic use of ginkgo for intermittent claudication (peripheral vascular disease), dementia (including Alzheimer’s disease), cerebrovascular insufficiency and tinnitus. There is strong evidence for use in age-associated memory impairment, memory enhancement in healthy individuals, altitude sickness, vertigo and premenstrual syndrome (PMS). Lastly, there is good evidence for use in macular degeneration.

During pregnancy, the main concern with using ginkgo leaf revolves around its antiplatelet activity as documented in animal studies. Although based on \textit{in vitro} evidence, there is a valid concern that ginkgo use could prolong bleeding during delivery. Based on this finding, it would be prudent to discontinue use of ginkgo weeks prior to delivery. In addition, patients and clinicians should be aware of manufacturers employing Good Manufacturing Practices (GMP) when choosing ginkgo products as a case series reported the adulteration of ginkgo with colchicine.

During lactation, ginkgo should be used with caution as there is no documentation in the scientific literature related to its safety during lactation.
With respect to ginkgo seed, theoretical evidence suggests that raw ginkgo seed should be avoided during pregnancy and lactation, while roasted ginkgo seed may possibly be safe if eaten in food amounts.

While traditional and common use has not indicated any substantive risks of taking this herb during pregnancy and lactation, clearly more rigorous and well-controlled research is needed in this area. Clinicians and patients should also be concerned about the potential for interactions that may occur between ginkgo and numerous prescription medications, particularly anticoagulant and antiplatelet drugs. This issue has greater significance when the possibility for increased exposure or toxicity to the developing fetus might result from altered drug metabolism due to interaction.
References


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<td>1c</td>
<td><strong>Good Scientific evidence</strong>&lt;br&gt;Evidence from one or more case series.</td>
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<td><em>In vitro scientific evidence</em>&lt;br&gt;Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
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<td>4</td>
<td><strong>INDIRECT evidence</strong>&lt;br&gt;Evidence based on scientific theory OR expert opinion.</td>
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6.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed Mills and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

6.3 Statement of significance and impact

Ginkgo is a popular NHP commonly used to support memory and cognitive function. To my knowledge, this is the first systematic review to examine the safety of ginkgo during pregnancy and lactation. Since the general population commonly uses ginkgo, there is the likelihood that a woman may be treated with ginkgo while unaware of being pregnant or that she is pregnant and begins ginkgo therapy assuming that ginkgo is natural and thereby safe. Examining the safety of ginkgo during pregnancy and lactation is clinically relevant.
7 Safety and efficacy of black cohosh (*Cimicifuga racemosa*) during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


7.1 Reference and manuscript

Title: Safety and efficacy of black cohosh (*Cimicifuga racemosa*) during pregnancy and lactation

Jean-Jacques Dugoua ND; Dugald Seely ND; Daniel Perri MD, BscPharm, FRCP(C); Gideon Koren MD; Edward Mills DPH, MSc

Abstract

**Background:** There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is the first article in a series that systematically reviews the evidence for common herbs used during pregnancy and lactation.

**Objectives:** To systematically review the literature for evidence on the use, safety, and pharmacology of black cohosh focusing on issues pertaining to pregnancy and lactation.

**Methods:** We searched 7 electronic databases and compiled data according to the grade of evidence found.
**Results:** We found varying levels of evidence on efficacy of use for different conditions and low-level evidence for harm during pregnancy and lactation.

**Conclusions:** Black cohosh shows evidence of being an effective aid in the treatment of menopausal symptoms. Black cohosh, alone or in combination with other medicinal herbs as “mother’s cordial”, has a long traditional use and is frequently used by midwives as a labour-inducing aid. Low-level evidence shows the following concerns of black cohosh use during pregnancy: 1) labour-inducing effects, 2) hormonal effects, 3) emmenagog properties and 4) anovulatory effects. Black cohosh should be used with caution during pregnancy, particularly during the first trimester. During lactation, there is low-level evidence of hormonal properties.

**Keywords:** Black cohosh, Cimicifuga racemosa, Actaea racemosa, pregnancy, lactation, breastfeeding, systematic review

**Introduction**

Black cohosh, latin names: *Actaea racemosa* and *Cimicifuga racemosa*, is a perennial plant member of the buttercup family that is native to North America. Black cohosh was originally used by Native American peoples in the treatment of many conditions, including gynaecologic disorders and musculoskeletal complaints. The most widely used and best studied commercial formulation available in the United States is Remifemin, a standardised extract of the rhizome. Numerous other brands of black cohosh are available, but not all are standardised extracts. Black cohosh should not be confused with the herb blue cohosh (*Caulophyllum thalictroides*), that is also used for gynaecologic disorders and has a much greater potential for toxicity.

The principal modern use of black cohosh relies on its purported efficacy in the treatment of menopausal symptoms, primarily hot flashes, sleep disturbances and depression. Its therapeutic activity has been attributed to claims that the herb has estrogenic properties. These claims, however, have been disputed. Black cohosh has also been used to treat dysmenorrhoea as recommended by the German Commission E.
There does not appear to be any indications of therapeutic or supportive use of this herb during pregnancy. Of concern however, is that the herb does have a reputation as being used traditionally as an herbal abortifacient. In addition, midwives have used black cohosh during labour for induction. As black cohosh is a common herb that is taken relatively commonly by women, and due to the potential for its usage during pregnancy, we undertook a systematic review of the literature on the efficacy of black cohosh for a number of indications as well as for its safety during pregnancy and lactation.

**Synonyms/Common Names/Related Substances**

Baneberry, black snakeroat, bugbane, bugwort, cimicifuga, macrotys, phytoestrogen, rattle root, rattle snakeroat, rattle top, rattlesnake root, rattleweed, snakeroat, squaw root, squawroot

**Constituents**

Triterpene glycosides (acetin, cimicifugoside, 27-deoxyacetin), organic acids (isofuronic acid, cimicifugic acids (A, B, E and F), fukinolic acid, caffeic acid, salicyic acid), cimicifugin, tannins, phytosterin

**Parts used**

Roots, rhizome

**Methods**

We searched the following databases from inception to June 2004: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common
name and Latin name of the herb were used as keywords along with “pregnancy”, “lactation” and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The grade of evidence for indications was evaluated as displayed in Table 1. We rated evidence of harm as displayed in Table 2.

Results

Indications for use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal symptoms\textsuperscript{11-13}</td>
<td>B1</td>
</tr>
<tr>
<td>Arthritis pain (with white willow bark, sarsaparilla, poplar bark and guaiacum resin)\textsuperscript{14}</td>
<td>B2</td>
</tr>
<tr>
<td>Induction of labour\textsuperscript{8}</td>
<td>E</td>
</tr>
</tbody>
</table>
## Safety of consumption during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induces labour(^8)</td>
<td>4</td>
</tr>
<tr>
<td>Hormonal effect (potentially estrogenic and/or anti-estrogenic)(^15)</td>
<td>4</td>
</tr>
<tr>
<td>Emmenagogue (especially in first trimester)(^10)</td>
<td>4</td>
</tr>
<tr>
<td>Anovulatory effects(^16)</td>
<td>4</td>
</tr>
</tbody>
</table>

A survey of midwives in the United States found that 45% of midwives use black cohosh to induce labour\(^8\). Black cohosh is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to black cohosh, mother’s cordial contains: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), blue cohosh (*Caulophyllum thalictroides*) and false unicorn (*Chamaelirium luteum*).

It is unclear if black cohosh has an estrogenic and/or an anti-estrogenic effect\(^15\). Nonetheless, a review article recommended that black cohosh be avoided during pregnancy due to its potential hormonal effect\(^15\).

A herbal contraindication and drug interaction compendium reported that black cohosh was an emmenagogue and contraindicated during pregnancy, particularly in the first trimester\(^10\).

A review article on the potential value of plants as sources of anti-fertility agents reported that black cohosh had anovulatory effects *in vitro*\(^16\).*
**Safety of consumption during lactation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hormonal effect (potentially estrogenic/anti-estrogenic)(^\text{15})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

It is unclear if black cohosh has an estrogenic and/or an anti-estrogenic effect\(^\text{15}\). Nonetheless, a review article recommended that black cohosh be avoided during lactation due to its potential hormonal effect\(^\text{15}\).

**Pharmacology**

In some studies, black cohosh constituents bind to estrogen receptors *in vitro* or have an estrogenic effect\(^\text{17-20}\). In other studies, black cohosh estrogenic or estrogen receptor-binding effects were not found\(^\text{21,22}\). Black cohosh antagonizes the proliferation of cells induced by estradiol *in vitro*, thereby having anti-estrogenic activity\(^\text{23}\). Black cohosh decreases luteinizing hormone (LH) levels, but has no effect on follicular stimulating hormone (FSH) levels\(^\text{19}\).

Black cohosh inhibits the growth of human breast cancer cells *in vitro*\(^\text{24,25}\). Black cohosh has anti-inflammatory effects\(^\text{26}\).

**Drug interactions**

- Docetaxel\(^\text{9}\)
- Doxorubicin\(^\text{9}\)
Discussion

There is strong scientific evidence for the use of black cohosh in the treatment of menopausal symptoms. In combination with other herbs, there is good evidence for the treatment of arthritis. During pregnancy, black cohosh has a long history of use for inducing labour; on its own or in combination with other medicinal herbs to make a formula referred to as “mothers cordial” or “partus preparatus”.

The level of evidence on the use of black cohosh during pregnancy is limited to theoretical evidence, a survey of midwives in the United States and to in vitro evidence. Although the quality of evidence is poor, there are concerns with black cohosh use during pregnancy, which can be summarized as 1) labour-inducing effects, 2) hormonal effects, 3) emmenagogue properties and 4) anovulatory effects. Black cohosh should be used with caution during pregnancy, particularly during the first trimester where the labour-inducing properties of black cohosh could be of greatest harm to the fetus. Despite no reports of malformations in the scientific literature, black cohosh should be used with caution in the third trimester and at delivery when used as a labour-inducing aid, until further clinical research is conducted.

The level of evidence for using black cohosh during lactation is also poor. Black cohosh should be used with caution as in vitro evidence suggests estrogenic/anti-estrogenic properties.

Traditional and common use has indicated a risk of taking this herb during pregnancy, particularly during the first trimester, and during lactation. Clearly more rigorous and well-controlled research is needed in this area.
References


<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><strong>Very Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.</td>
</tr>
<tr>
<td>B1</td>
<td><strong>Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).</td>
</tr>
<tr>
<td>B2</td>
<td><strong>Good scientific evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.</td>
</tr>
<tr>
<td>C</td>
<td><strong>Fair Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more cohort studies OR outcome studies.</td>
</tr>
<tr>
<td>D</td>
<td><strong>Weak Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case series.</td>
</tr>
<tr>
<td>E</td>
<td><strong>INDIRECT and/or Clinical evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case reports OR expert opinion OR laboratory studies.</td>
</tr>
<tr>
<td>F</td>
<td><strong>Historical or traditional evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.</td>
</tr>
<tr>
<td>Level</td>
<td>Evidence</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>1a</td>
<td><strong>Very Strong scientific evidence</strong>&lt;br&gt;Statistically significant evidence from one or more systematic reviews or RCTs.</td>
</tr>
<tr>
<td>1b</td>
<td><strong>Strong Scientific evidence</strong>&lt;br&gt;Statistically significant evidence from one or more cohort studies OR case control study.</td>
</tr>
<tr>
<td>1c</td>
<td><strong>Good Scientific evidence</strong>&lt;br&gt;Evidence from one or more case series.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Fair Scientific evidence</strong>&lt;br&gt;Evidence based on case reports.</td>
</tr>
<tr>
<td>3</td>
<td><strong>In vitro scientific evidence</strong>&lt;br&gt;Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
</tr>
<tr>
<td>4</td>
<td><strong>INDIRECT evidence</strong>&lt;br&gt;Evidence based on scientific theory OR expert opinion.</td>
</tr>
<tr>
<td>5</td>
<td><strong>Unknown</strong>&lt;br&gt;No available information.</td>
</tr>
</tbody>
</table>
7.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed Mills, Dugald Seely and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

7.3 Statement of significance and impact

Black cohosh is a common NHP used in women’s health, particularly menopausal symptoms. Pharmacologically, black cohosh has estrogenic properties, which would explain why it is used clinically for women’s health issues such as infertility, premenstrual syndrome, dysmenorrhea and others. Black cohosh is also commonly used by midwives to support labour. To my knowledge, this is the first systematic review to examine the safety of black cohosh in pregnancy and lactation. Examining the safety of black cohosh during pregnancy and lactation is clinically relevant.
8 Safety and efficacy of blue cohosh (Caulophyllum thalictroides) during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


8.1 Reference and manuscript

Title: Safety and efficacy of blue cohosh (Caulophyllum thalictroides) during pregnancy and lactation

Jean-Jacques Dugoua, Daniel Perri, Dugald Seely, Edward Mills, Gideon Koren

Abstract

Background: There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines in pregnancy and lactation. This is one article in a series that systematically reviews the evidence for commonly used herbs during pregnancy and lactation.

Objectives: To systematically review the literature for evidence on the use, safety, and pharmacology of blue cohosh focusing on issues pertaining to pregnancy and lactation.

Methods: We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results: According to a survey of midwives in the United States, approximately 64% of midwives reported using blue cohosh as a labour-inducing aid. There are three case reports in the scientific literature that blue cohosh taken at the time of delivery may cause 1) perinatal stroke,
2) acute myocardial infarction, profound congestive heart failure and shock and 3) severe multi-organ hypoxic injury. There is one case report that blue cohosh possesses abortifacient properties. There is in vitro evidence that blue cohosh may have teratogenic, embryotoxic and oxytocic effects. In lactation, the safety of blue cohosh is unknown.

**Conclusions:** Based on the available scientific information, blue cohosh should be 1) used with extreme caution during pregnancy, 2) used only under medical professional supervision and 3) not be available to the public as an over-the-counter product. There is an urgent need to conduct a retrospective or prospective cohort study of midwives using blue cohosh in order to determine its safety.

**Keywords:** Blue cohosh, *Caulophyllum thalictroides*, pregnancy, lactation, breastfeeding, systematic review

**Introduction**

Blue Cohosh (*Caulophyllum thalictroides*) is a small woodland perennial plant with large blue berries that is native to the American north-east. Although they are named similarly, blue cohosh should not be confused with black cohosh (*Actea racemosa*), which is actually from a separate botanical genus. The medicinal effects of blue cohosh are derived from its root and rhizomes. Blue cohosh is also referred to as “papoose root” or “squaw root”, which reflects the use of this herbal medicine by Native American women who brewed blue cohosh as a tea to relieve menstrual cramps and to ease the pains associated with childbirth.

Between 1882 and 1905, blue cohosh was listed in the *United States Pharmacopoeia* as a labor inducer\(^1\). Blue cohosh is often part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In a 1999 survey of Certified Nurse Midwives in the United States, 64% claimed to use blue cohosh during labour\(^1\). Currently, blue cohosh is used to induce labour, to help speed the process of labour, and generally to help the mother through labour as quickly and painlessly as possible\(^1\)-\(^3\).
Given the historical and modern use of blue cohosh, we have conducted a systematic review of the literature to assess the efficacy of blue cohosh and its potential for harm to both mother and fetus during pregnancy, labour and lactation.

**Synonyms/Common Names/Related Substances**

Blue ginseng, caulophyllum, papoose root, squaw root, yellow ginseng

**Constituents**

Triterpene saponins: caulophylogenin, hederagenin, caulosaponin

Alkaloids: thalictroidine, taspine, magnoflorine, anagyrine, baptifoline, 5,6-dehydro-alpha-isolupanine, alpha-isolupanine, lupanine, N-methylcytisine, sparteine

**Parts used**

Rhizome and root

**Methods**

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyze all the relevant scientific medical literature that provide information as to the safety, efficacy and pharmacology of blue cohosh in pregnancy and lactation. Our strategy employed systematic searching of the following databases from inception to March 2007: AMED, CINAHL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Controlled Trials Database, MedLine, E-Psyche, AltHealthWatch and DARE. The MeSH terms used for searching included the common and Latin name of the herb along with “pregnancy”, “lactation”
and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search. To ensure that reports, trials and other forms of evidence were not overlooked, the following additional databases were consulted: Complete German Commission E Monographs by the American Botanical Council, Natural Database and Natural Standard.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The efficacy of blue cohosh was evaluated according to the grade of evidence for indications presented in Table 1. The safety in pregnancy and lactation of blue cohosh was evaluated according to the evidence level for harm presented in Table 2.
Results

Indications for use

<table>
<thead>
<tr>
<th>Induction of labour(^1)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
</tr>
</tbody>
</table>

A survey of midwives in the United States found that 64% of midwives use blue cohosh to induce labour\(^1\). Blue cohosh is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to blue cohosh, mother’s cordial may contain: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), black cohosh (*Cimicifuga racemosa*) and false unicorn (*Chamaelirium luteum*).

Blue cohosh was identified by the midwives surveyed as the herbal medicine used in pregnancy with the lowest comfort level as based on a scale from 0 to 10\(^1\). The midwives reported adverse effects that are usually attributed to blue and black cohosh as nausea, increased meconium-stained fluid and transient fetal tachycardia\(^1\). When inducing labour, the midwives also reported that blue cohosh was typically administered as a tincture at the following dosage: 5 drops every 4 hours or 10 drops in hot water every 2 hours\(^1\).
Safety of consumption during pregnancy

**Herbal preparation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear if causal relationship - Perinatal stroke</td>
<td>2</td>
</tr>
<tr>
<td>Acute myocardial infarction, profound congestive heart failure and shock</td>
<td>2</td>
</tr>
<tr>
<td>Severe multi-organ hypoxic injury</td>
<td>2</td>
</tr>
<tr>
<td>Abortifacient</td>
<td>2</td>
</tr>
<tr>
<td>Uterine stimulant</td>
<td>2</td>
</tr>
<tr>
<td>May induce nicotinic toxicity</td>
<td>2</td>
</tr>
<tr>
<td>Potentially teratogenic (contains anagyrine)</td>
<td>2</td>
</tr>
<tr>
<td>Embryotoxic</td>
<td>3</td>
</tr>
<tr>
<td>Induces labour</td>
<td>4</td>
</tr>
<tr>
<td>Emmenagogue</td>
<td>4</td>
</tr>
<tr>
<td>Oxytocic</td>
<td>4</td>
</tr>
</tbody>
</table>

Finkel & Zarlengo (2004) reported a case in the New England Journal of Medicine (NEJM) of a healthy 24-year-old woman (gravida 2, para 0) who was advised by her obstetrician to drink a tea made from blue cohosh to induce labour. Following a failed vaginal delivery leading to a cesarean section at 40 weeks, a female infant was born weighing 3860g with focal motor seizures of the right arm, which began at 26 hours of age, and which were controlled with phenobarbital and phenytoin. A computed tomography (CT) scan of the infant at two days of age showed an evolving infarct in the distribution of the left middle cerebral artery. After thrombophilia studies and medical history, the newborn showed no evidence of innate tendency nor family
history of excessive blood clotting. Urine and meconium samples, however, were positive for the cocaine metabolite benzoylecgonine on screening by immunoassay and were confirmed by gas chromatography-mass spectrometry. The presence of benzoylecgonine was confirmed in the mother's bottle of blue cohosh and in a sealed bottle of a different preparation of the tea administered.

In letters to the NEJM Editor, a number of issues were raised as to the validity of a causal relationship between blue cohosh and the cocaine metabolite benzoylecgonine. Potterton (2004) reported that the suggestion that blue cohosh might produce cocaine metabolites is not plausible, given what is known about the plant's chemistry. Chan & Nelson (2004) reported that there is no published evidence that blue cohosh contains benzoylecgonine or a product that is metabolized to benzoylecgonine; they suggest that the presence of benzoylecgonine in the newborn most likely represents either exposure to a tea containing coca leaves (Erythroxylon coca) or to cocaine use by the mother.

In their response, Finkel & Zarlengo (2004) agreed that blue cohosh is not known to contain benzoylecgonine or to be metabolized to this cocaine metabolite, and stated that neither adulteration of benzoylecgonine by cocaine or Inca tea nor maternal cocaine use was supported for this case. They reported that the results may have reflected detection of a cross-reacting substance by an insensitive immunoassay, an incorrect interpretation of the gas chromatography–mass spectrometry data by the reference laboratory, or both. Although benzoylecgonine has direct vasoactive properties, presenting another plausible pathophysiologic mechanism for stroke, it is unclear if the positive toxicologic finding of benzoylecgonine was the sole potential explanation for the neonate's stroke, but rather a confounding issue.

One case was reported of an infant born with acute myocardial infarction, profound congestive heart failure and shock as a result of the mother ingesting blue cohosh to promote uterine contractions. The infant remained critically ill for several weeks and eventually recovered. The authors reported that all other causes of myocardial infarction were carefully excluded. The
authors believed that these observed effects were due to the vasoactive glycosides and an alkaloid of blue cohosh known to produce toxic effects on the myocardium. Another case was reported of severe multi-organ hypoxic injury in a child delivered "naturally" with the aid of both blue and black cohosh who was not breathing at the time of birth. The child survived with permanent central nervous system damage. Blue cohosh which possesses a vasoconstrictive glycoside, and not black cohosh, was believed to be responsible for the adverse effects.

A 21-y-old female developed signs of nicotinic toxicity, i.e., tachycardia, diaphoresis, abdominal pain, vomiting and muscle weakness and fasciculations, after using blue cohosh in an attempt to induce an abortion. The saponins in blue cohosh are believed to be responsible for the uterine stimulant effect. A review article on the potential value of plants as sources of anti-fertility agents also reported that blue cohosh was a potential abortifacient, emmenagogue and uterine stimulant.

The alkaloid anagyrine, which is found in the root of blue cohosh, has been held responsible for the congenital deformity “crooked calf disease”. This disease is found in bovine stock but could not be reproduced in sheep or hamsters. The severity of the deformity was found to be directly related to the concentration of anagyrine in the extracts used. There is also a case report of a similar human congenital malformation (marked anemia, skeletal dysplasia, and vascular anomaly) in an infant, which could have been due to maternal exposure to anagyrine contamination of goat milk in early pregnancy.

The alkaloid methylcytisine, a constituent of blue cohosh, was shown to be teratogenic in rats. The alkaloid taspine, a constituent of blue cohosh, was shown to be highly embryotoxic in rats. A compendium for medicinal plants reported that blue cohosh may have oxytocic effects.
**Homeopathic Blue Cohosh (Caulophyllum)**

<table>
<thead>
<tr>
<th>Does not induce labour\textsuperscript{17, 18}</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
</tr>
</tbody>
</table>

A systematic review concluded that there is insufficient evidence to recommend the use of homeopathic blue cohosh as a method of inducing labour\textsuperscript{17, 18}. Although caulophyllum is a commonly used homeopathic therapy to induce labour, the treatment strategy used in this review may not reflect routine practice of homeopathy. A homeopathic preparation of *Caulophyllum thalictroides*, called Caulophyllum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance.

**Safety of consumption during lactation**

<table>
<thead>
<tr>
<th>Possible cardiotoxic effects\textsuperscript{8}</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals\textsuperscript{8}. Blue cohosh is not reported in the evidence-based medicine literature as being either contraindicated or safe in lactation.

**Toxicology**

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals\textsuperscript{8}. Blue cohosh may constrict coronary arteries and decrease the flow of oxygen to the heart\textsuperscript{19}. The alkaloid methylcytisine was shown to cause symptoms of nicotinic toxicity and teratogenic in rats\textsuperscript{7}. The alkaloid taspine was shown to be embryotoxic in rats\textsuperscript{7}. 
Pharmacology

Blue cohosh enhances estradiol binding to estrogen receptors and increases estradiol-induced transcription activity in estrogen-responsive cells\(^4\). Blue cohosh decreases luteinizing hormone (LH) levels and increases serum ceruloplasmin oxidase activity, which are measures of estrogenic activity in the liver\(^4\).

On the excised uteri of guinea pigs, blue cohosh was found to contain the only active oxytocic responsible for increasing uterine tone\(^20\). Blue cohosh frequently initiated contractions in non-active strips of uterine tissue but also increased tone with cessation of contractions, which the authors described as tetanus\(^20\). Although a decrease in blood pressure of 30–50 mm with a “fairly prompt” return to normal was observed when blue cohosh was administered to dogs in large doses, a subsequent \textit{in vivo} study also on dogs indicated no effect on the uterus when blue cohosh was administered in high doses\(^21\).

Drug interactions

Anti-diabetic Drugs\(^4\)

Cardiovascular Drugs\(^5, 8\)

Nicotine\(^7\)

Discussion

In the evidence-based literature, the main, if not only, therapeutic indication of blue cohosh is as an agent to stimulate labour. Unfortunately, this therapeutic indication is based on low quality evidence from a survey of midwives in the United States where approximately 64\% of the respondents reported that they use blue cohosh as a labour-inducing aid, and on a few \textit{in vitro}
studies where blue cohosh has demonstrated a uterine stimulating effect on animal uteri. Homeopathic blue cohosh, however, was not shown to be a conclusive method of inducing labour according to a systematic review.

There are three case reports that blue cohosh taken at the time of delivery may cause 1) perinatal stroke, 2) acute myocardial infarction, profound congestive heart failure and shock and 3) severe multi-organ hypoxic injury. As blue cohosh can have a toxic effect on cardiac muscle, probably due to its vasoconstrictive activity on coronary vessels, it is plausible that blue cohosh may have been the causative factor for these observed cardiovascular birth defects. In both case reports of acute myocardial infarction, profound congestive heart failure, shock and severe multi-organ hypoxic injury, the authors imply a causative relationship between blue cohosh intake by the mother and their cardiac toxicity findings. In the case report of perinatal stroke, however, a causal relationship was unclear due to the confounding presence of benzoylgonine, a cocaine metabolite, in urine and meconium samples. In their correspondence with the editor, the authors of this case appeared to have ruled out cocaine use by the mother and adulteration of the blue cohosh product used; rather, they attributed their findings to a laboratory instrument or analysis error, which is being further investigated. Nonetheless, blue cohosh remains a suspect as the causative factor in perinatal stroke. Lastly, further evidence of cardiac toxicity was observed in the midwife survey where it was reported that one of the most common adverse effect associated with blue and black cohosh administration at delivery was fetal tachycardia; as black cohosh has not been documented as having cardiac effects or as containing cardiac glycosides, it would appear that blue cohosh would be responsible for this adverse effect.

On the other hand, 64% of surveyed midwives reported using blue cohosh during delivery. It would seem likely that these licensed and trained medical professionals would not be administering a therapeutic agent that may cause severe cardiac adverse events to their patients or patients’ newborns. Unfortunately, there is no evidence in the scientific literature on the safe use of blue cohosh by midwives during pregnancy. Of interest, however, and as evidence that blue cohosh is perhaps used with caution by midwives is the report that blue cohosh was the herbal medicine used in pregnancy with the lowest comfort level.
Perhaps the cases reported above are due to blue cohosh being administered outside of its therapeutic window? Evidence to support a dose-dependant relationship was reported in the midwife survey where there was a wide variation in doses and number of doses for administering blue cohosh at delivery. As midwives reported learning about the use of herbal therapies by “word-of-mouth” from other midwives and not from research or specific texts, it may be plausible that whenever they use blue cohosh, they administer it at dosages within its therapeutic window.

There is fair evidence based on a case report that blue cohosh possesses abortifacient properties. Theoretical and/or expert opinion evidence lend support to this observation as blue cohosh is also listed as a potential abortifacient, emmenagogue and uterine stimulant. Of concern, however, is a report of nicotinic toxicity associated with the use of blue cohosh to induce abortion. Although it appears that blue cohosh was administered outside of its therapeutic window in this case, clinicians should be made aware of the potential of blue cohosh to cause nicotinic toxicity.

Based on in vitro evidence, blue cohosh may have teratogenic, embryotoxic and oxytoxic effects. Of concern is the presence of anagyrine in blue cohosh, which is believed to be responsible for the congenital deformity “crooked calf disease” in bovine animals. Although this teratogenic effect was not observed in sheep or hampsters, a case was documented of a human infant with similar congenital malformations (marked anemia, skeletal dysplasia and vascular anomaly) following maternal exposure to anagyrine-contaminated goat milk in early pregnancy.

In lactation, the safety of blue cohosh is unknown. It is unclear if the cardiac glycosides would cross into breast milk and potentially cause cardiovascular adverse effects in the newborn. It should be noted, however, that blue cohosh is mostly used to stimulated labour and would most likely be discontinued after delivery; thereby it would appear unlikely that lactating mothers
would consume this herb. Nonetheless, blue cohosh should be avoided in lactation until further high quality research is conducted.

Based on case reports of cardiac toxicity, abortive effects, nicotinic toxicity and potential teratogenicity, blue cohosh should be 1) used with extreme caution during pregnancy, 2) used only under medical professional supervision and 3) not be available to the public as an over-the-counter product. Blue cohosh should be avoided particularly during the first trimester due to case reports of abortifacient and teratogenic properties. The use of blue cohosh should be restricted to medical professionals trained in its administration at delivery, such as obstetricians, midwives, naturopathic doctors and medical herbalists to name a few. As natural health products are frequently unregulated, governmental agencies should take immediate steps to limit public access to blue cohosh in order to prevent the administration of this herb without the supervision of a licensed and trained medical professional. There is an urgent need to conduct a retrospective or prospective cohort study of midwives using blue cohosh in order to determine its safety at the time of delivery as any scientific evidence of safety or harm is more likely to be in the files of the midwifery practices than in governmental databases or hospitals.

References


Table 1. Levels of evidence for efficacy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><strong>Very Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.</td>
</tr>
<tr>
<td>B1</td>
<td><strong>Strong Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).</td>
</tr>
<tr>
<td>B2</td>
<td><strong>Good scientific evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.</td>
</tr>
<tr>
<td>C</td>
<td><strong>Fair Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence of benefit from one or more cohort studies OR outcome studies OR case control studies.</td>
</tr>
<tr>
<td>D</td>
<td><strong>Weak Scientific Evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case series.</td>
</tr>
<tr>
<td>E</td>
<td><strong>INDIRECT and/or Clinical evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Evidence from case reports OR expert opinion OR laboratory studies.</td>
</tr>
<tr>
<td>F</td>
<td><strong>Historical or traditional evidence</strong></td>
</tr>
<tr>
<td></td>
<td>Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.</td>
</tr>
</tbody>
</table>
Table 2. Levels of evidence for harm

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Very Strong scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence from one or more systematic reviews or RCTs.</td>
</tr>
<tr>
<td>1b</td>
<td>Strong Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Statistically significant evidence from one or more outcome studies OR cohort studies OR case control studies.</td>
</tr>
<tr>
<td>1c</td>
<td>Good Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence from one or more case series.</td>
</tr>
<tr>
<td>2</td>
<td>Fair Scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on case reports.</td>
</tr>
<tr>
<td>3</td>
<td>In vitro scientific evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
</tr>
<tr>
<td>4</td>
<td>Theoretical evidence</td>
</tr>
<tr>
<td></td>
<td>Evidence based on scientific theory OR expert opinion.</td>
</tr>
<tr>
<td>5</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>No available information.</td>
</tr>
</tbody>
</table>
8.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed Mills, Dugald Seely and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

8.3 Statement of significance and impact

Blue cohosh has a long herbal tradition of use as a supporting agent during labour. To my knowledge, this is the first systematic review to examine the safety of blue cohosh during pregnancy and lactation. This systematic review identified a number of case reports associated with adverse effects of blue cohosh use during pregnancy. Examining the safety of blue cohosh during pregnancy and lactation is clinically relevant.
9  Safety and efficacy of Chastetree (*Vitex agnus-castus*) during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


### 9.1 Reference and manuscript

**Title:** Safety and efficacy of Chastetree (*Vitex agnus-castus*) during pregnancy and lactation

Jean-Jacques Dugoua HBSc ND PhD (cand.); Dugald Seely ND; Daniel Perri MD BscPharm FRCP(C); Gideon Koren MD; Edward Mills DPH MSc PhD

**Abstract**

**Background:** There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

**Objectives:** To systematically review the literature for evidence on the use, safety, and pharmacology of chastetree focusing on issues pertaining to pregnancy and lactation.

**Methods:** We searched 7 electronic databases from inception to June 2006 and compiled data according to the grade of evidence found.
**Results:** In pregnancy, there is poor evidence based on theoretical and expert opinion and *in vitro* studies that chastetree may have estrogenic and progesteronic activity, uterine stimulant activity, emmenagogue activity and prevent miscarriages. In lactation, theoretical and expert opinion conflict as to whether chastetree increases or decreases lactation.

**Conclusions:** Given its relatively common use amongst women of childbearing age, it is likely that some women may consume chastetree while unknowingly pregnant. Complementary and alternative medicine, midwifery, and medical practitioners should be aware of this fact when prescribing chastetree to women of childbearing age, particularly when the patient is planning a family.

**Introduction**

Chastetree, a deciduous shrub native to Mediterranean Europe, central Asia, and parts of India, has a long history of use dating as far back as the ancient Greeks and Romans. The Latin name for chastetree is *Vitex agnus-castus*, an allusion to its usage in the preservation of chastity. The fruits of chastetree contain a mixture of iridoids and flavonoids, and some compounds isolated from the leaves and flowers were found to be similar in chemical structure to human sex hormones [1, 2].

Chastetree has been used for centuries for a variety of gynecologic conditions, including premenstrual syndrome, cyclical mastalgia, and menstrual irregularities [3]. Today, the German Commission E, a panel of experts charged with evaluating the safety and efficacy of the herbs available in pharmacies for general use, has approved chastetree for the gynecologic conditions previously cited[4]. Medical doctors in Germany frequently prescribe chastetree to patients and it is used commonly throughout Europe and North America [5].

The principal activity of chastetree appears to be derived from dopaminergic compounds present in the herb that improve premenstrual mastodynia and possibly other symptoms of premenstrual
syndrome [2]. Evidence indicates that an extract of chastetree binds to dopamine (D2) receptors in the hypothalamus and anterior pituitary, thereby inhibiting the release of prolactin and thus reducing corresponding mastalgia. Other endocrine effects appear to occur, including increased progesterone secretion and induction of normal formation of the corpus luteum [6].

There are claims that chastetree may enhance female fertility. As such, there is a strong likelihood that women may take this herb while unknowingly pregnant. A crossover period of taking chastetree while pregnant may be likely, which is of concern for the fetus given its susceptibility to teratogenic influences during the first trimester [7]. We have systematically searched the literature in order to assess for safety, efficacy, pharmacology and drug-herb interactions of *Vitex agnus castus* with an emphasis on issues relating to pregnancy and lactation.

**Synonyms/common names**

Agnolyt, agnus castus, agnus-castus, chaste berry, chaste tree, chaste tree berry, chastetree, gattilier, hemp tree, monk's pepper, vitex, *Vitex agnus castus* [8]

**Constituents:**

Essential oils: limonene, cineol, pinene, and sabinene [9]

Iridoid glycosides: aucubin and agnoside [10, 11]

Flavonoids: casticin, kaempferol, quercetagetin, orientin, and isovitexin [9, 11]

Diterpenes: vitexilactone, rotundifuran, and 6-beta,7 beta-diacetoxy-13-hydroxy-labda-8,14-dien [9, 10, 12, 13]

Essential fatty acids: oleic acid, linolenic acid, palmitic acid, and stearic acid [13]
**Part used:**

Fruit [14]

**Methods**

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provide information as to the safety, efficacy and pharmacology of chastetree in pregnancy and lactation. We searched the following databases from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as key words along with “pregnancy”, “lactation” and “breastfeeding”. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The grade of evidence for indications was evaluated as displayed in Table 1. We rated evidence of harm as displayed in Table 2.

**Results**

**Indications for use**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic mastalgia [21, 22]</td>
<td>B1</td>
</tr>
<tr>
<td>Hyperprolactinemia [23]</td>
<td>B1</td>
</tr>
</tbody>
</table>
Infertility (homeopathic preparation) [24] | B1
---|---
Menstrual disorders [11, 17] | E

### Use and safety during pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level of evidence for potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases progesterone (homeopathic preparation) [24]</td>
<td>1a</td>
</tr>
<tr>
<td>Estrogenic and progesteronic activity [26]</td>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant [8]</td>
<td>4</td>
</tr>
<tr>
<td>Emmenagogue [27]</td>
<td>4</td>
</tr>
</tbody>
</table>

A prospective, randomised, placebo-controlled, double-blind study was conducted on a homeopathic preparation of chastetree for women with fertility disorders [24]. The researchers observed a non-significant increase in fertility and a significant increase of progesterone during the luteal phase [24]. Lower level evidence using Chastetree as a herbal preparation also indicates that it may have estrogenic and progesterone activity [26].

Compendia of drug interactions and safety on natural products report that chastetree is a uterine stimulant and an emmenagogue [8, 27]. No reports in the evidence-based literature of chastetree being a uterine stimulant or as an emmenagogue were found in our search, however.
A compendium on herbal medicine reported that chastetree is used by some clinicians during the first trimester of pregnancy to prevent miscarriages in patients with progesterone deficiency [11]. No reports in the peer reviewed medical literature indicate that chastetree actually prevents miscarriages through this, or any other, mechanism.

**Use and safety during lactation**

<table>
<thead>
<tr>
<th></th>
<th>Level of evidence for potential harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases lactation [9, 11, 13]</td>
<td>4</td>
</tr>
<tr>
<td>Decreases lactation [17]</td>
<td>4</td>
</tr>
</tbody>
</table>

Compendia on herbal medicine and a plant monograph report that chastetree increases lactation [9, 11, 13]. There was one additional source reporting that chastetree decreases lactation due to the suppression of prolactin production [17].

**Toxicity and adverse effects**

In a recently conducted systematic review of adverse events of chastetree used as single treatment, it was found that side effects potentially caused by *Vitex agnus castus* were mild and reversible [28]. The most frequently cited adverse events include: nausea, mild gastrointestinal complaints, fatigue, menstrual disorders, dry mouth, acne, pruritus, and erythematous rash [5, 28]. There was one report of a case of nocturnal seizures in a patient taking a combination of herbs that included chastetree, however it is unlikely that vitex was the causative agent [5, 29].

**Pharmacology**

There is some evidence that chastetree may have hormonal properties through estrogenic and progesterone activity, however the evidence is limited [26]. It is claimed that compounds in chastetree selectively bind to beta estrogen receptors in the heart, vasculature, bone, and bladder
Chastetree may affect dopamine, acetylcholine and opioid receptors [12]. In high doses, chastetree has agonist effects on pituitary dopamine (D2) receptors [1, 30]. In women with hyperprolactinemia, evidence suggests that chastetree suppresses prolactin release and normalizes luteal phase defects in the menstrual cycle [23].

Chastetree does not appear to affect testosterone levels [31]. In vitro work suggests that vitex may inhibit the growth of breast, ovarian, cervical, gastric, colon and lung cancer cells [32, 33]. Essential oils derived from this herb have demonstrated antibacterial and antifungal properties [11].

**Drug Interactions**

The likelihood of drug interactions resulting from chastetree consumption is relatively low. However, this herb is contraindicated for use in conjunction with drugs used to treat Parkinson’s disease, such as bromocriptine and metaclopramide [2, 30]. In addition, concurrent use of antipsychotic drugs is contraindicated [1, 30] as are any dopamine agonists [1, 12, 30]. Caution is suggested with oral contraceptives and during hormone replacement therapy [34].

**Discussion**

There is strong scientific evidence that chastetree may be beneficial for the treatment of premenstrual syndrome, cyclical mastalgia and hyperprolactinemia. There is good scientific evidence of efficacy for the treatment of infertility. As an ingredient of a homeopathic preparation, chastetree was not shown to be significantly effective in treating infertility, but did increase progesterone secretion.

In pregnancy, there is poor evidence based on theoretical and expert opinion and *in vitro* studies that chastetree may have estrogenic and progesteronic activity, uterine stimulant activity,
emmenagogue activity and prevent miscarriages. As such, the safety of chastetree during pregnancy remains unclear until human studies are conducted to validate its safe use for both the mother and unborn child. Given its relatively common use amongst women of childbearing age, it is likely that some women may consume chastetree while unknowingly pregnant, as approximately half of all pregnancies are unplanned. Complementary and alternative medicine, midwifery, and medical practitioners should be aware of this fact when prescribing chastetree to women of childbearing age, particularly when the patient is planning a family.

In the case of lactation, theoretical and expert opinion conflict as to whether chastetree increases or decreases lactation. There are no reports in the scientific literature to suggest that compounds from this herb cross into the breast milk. The low toxicity profile and tolerability of chastetree makes it unlikely to be toxic for the newborn, especially after filtration and dilution through the mother. Nonetheless, caution is warranted with its use as chastetree has phytoestrogenic and phytoprogesteronic properties. More human research is warranted to determine the action of chastetree on breast milk production; until then, it should be used with caution.

Further research should focus on the pharmacokinetics of this herb as well as to what degree constituents are able to cross the placental barrier into the fetus and cross into breast milk. This herb appears safe for general use, but it is important that we know more regarding its level of safety and possible therapeutic roles with respect to the breastfeeding mother and, especially, the expectant mother.

**Acknowledgements**

The Canadian College of Naturopathic Medicine, Motherisk – Sick Kids Hospital, University of Toronto and McMaster University
<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
</table>
| A     | **Very Strong Scientific Evidence**  
Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis. |
| B1    | **Strong Scientific Evidence**  
Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs). |
| B2    | **Good scientific evidence**  
Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies. |
| C     | **Fair Scientific Evidence**  
Statistically significant evidence of benefit from one or more cohort studies OR outcome studies. |
| D     | **Weak Scientific Evidence**  
Evidence from case series. |
| E     | **INDIRECT and/or Clinical evidence**  
Evidence from case reports OR expert opinion OR laboratory studies. |
| F     | **Historical or traditional evidence**  
Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups. |
Table 2. Levels of evidence for potential harm

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td><strong>Very Strong scientific evidence</strong>&lt;br&gt;Statistically significant evidence from one or more systematic reviews or RCTs.</td>
</tr>
<tr>
<td>1b</td>
<td><strong>Strong Scientific evidence</strong>&lt;br&gt;Statistically significant evidence from one or more cohort studies OR control study.</td>
</tr>
<tr>
<td>1c</td>
<td><strong>Good Scientific evidence</strong>&lt;br&gt;Evidence from one or more case series.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Fair Scientific evidence</strong>&lt;br&gt;Evidence based on case reports.</td>
</tr>
<tr>
<td>3</td>
<td><strong>In vitro scientific evidence</strong>&lt;br&gt;Evidence based on scientific studies conducted on animals, insects or micro-organisms OR laboratory studies on human cells.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Theoretical evidence</strong>&lt;br&gt;Evidence based on scientific theory OR expert opinion.</td>
</tr>
<tr>
<td>5</td>
<td><strong>Unknown</strong>&lt;br&gt;No available information.</td>
</tr>
</tbody>
</table>
References


9.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed Mills, Dugald Seely and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

9.3 Statement of significance and impact

Chastetree is a common herb used by women for premenstrual syndrome and cystic mastalgia. To my knowledge, this is the first systematic review to examine the safety of chastetree during pregnancy and lactation. Since a woman may be unknowingly pregnant and undergoing chastetree treatment, there is a need to ascertain its safety during pregnancy.
10 Safety and efficacy of cranberry (*Vaccinium macrocarpon*) during pregnancy and lactation

Published as a manuscript in the Canadian Journal of Clinical Pharmacology. The full reference is follows:


10.1 Reference and manuscript

Title: Safety and efficacy of cranberry (*Vaccinium macrocarpon*) during pregnancy and lactation

Jean-Jacques Dugoua, HBSc ND PhD (cand.); Dugald Seely, ND; Daniel Perri, MD BscPharm FRCP(C); Edward Mills, DPH MSc PhD; Gideon Koren, MD

Abstract

**Background:** There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

**Objectives:** To systematically review the literature for evidence on the use, safety, and pharmacology of cranberry focusing on issues pertaining to pregnancy and lactation.

**Methods:** We searched 7 electronic databases and compiled data according to the grade of evidence found.
Results: There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. Indirectly, there is good scientific evidence that cranberry may be of minimal risk where a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of cranberry is unknown.

Conclusions: Women experience urinary tract infections with greater frequency during pregnancy. Given the evidence to support the use of cranberry for urinary tract infections (UTIs) and its safety profile, cranberry supplementation as fruit or fruit juice may be a valuable therapeutic choice in the treatment of UTIs during pregnancy.

Introduction

American cranberry (Vaccinium macrocarpon) is one of the few fruits native to Eastern North America. It is also found in Northern Europe. Traditional medicinal use of cranberry fruit by Native Americans was primarily for the treatment of bladder and kidney ailments [1]. There has also been a relatively long history of scientific research on this herbal remedy dating back to its chemical characterization in the late 19th century [2]. Cranberry’s principal therapeutic value today continues to be for the treatment and prevention of urinary tract infections [3].

It was originally thought that cranberry’s biological activity was due to an acidifying effect on urine, however, this theory has been largely disproved [1]. The currently accepted mechanism of action in treating and preventing urinary tract infections is through disabling Escherichia coli’s capacity to adhere to the urethra[2, 4]. The fruit contains two compounds, fructose and a proanthocyanidin, that adhere to proteins on the fimbriae of E. coli, effectively inhibiting the bacteria from sticking to the epithelial cell lining of the urethra [2, 4]. Without the ability to establish a strong foothold via adherence, the infection is either attenuated or prevented at the outset.
The pregnant woman, along with a number of other issues, has to deal with an increased frequency of urinary tract infections [5, 6]. Given the recognised safety of cranberry juice and its efficacy in the treatment of urinary tract infections [2, 7], it is of no surprise that this therapy is widely used by pregnant women. A survey of 400 women from Norway found that cranberry fruit juice was the most commonly used herbal therapy during pregnancy [8]. The popular use of this herb during pregnancy calls for an in-depth understanding of its efficacy and potential for harm during pregnancy and lactation. We have endeavoured to address these issues in a systematic review of the literature.

Synonyms/ Common names

American cranberry, arandano Americano, arandano trepador, cranberries, European cranberry, grosse moosbeere, kranbeere, canneberge, large cranberry, moosebeere, mossberry, ronce d'Amerique, small cranberry, trailing swamp cranberry, tsuru-kokemomo, vaccinium, vaccinium macrocarpon [9]

Constituents

Proanthocyanidins, triterpenoids, lectins, catechins, ascorbic acid, benzoic acid, quinic acid, oxalic acid, citric acid, and malic acid [10]

Part used

Fruit [9]

Methods

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provide information as to the safety,
efficacy and pharmacology of cranberry in pregnancy and lactation. We searched the following databases from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as the key words along with “pregnancy”, “lactation” and “breastfeeding”. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in the final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm is rated as displayed in Table 2.

**Results**

**Indications for use**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of stomach ulcers [12, 13]</td>
<td>E</td>
</tr>
<tr>
<td>Prevention of periodontal disease [14-16]</td>
<td>E</td>
</tr>
<tr>
<td>Influenza prevention [17]</td>
<td>E</td>
</tr>
</tbody>
</table>
Use and safety during pregnancy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Commonly used without evidence of harm [8, 18]</th>
<th>1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Minimal risk (taken as food) [19]</td>
<td></td>
</tr>
</tbody>
</table>

A survey was conducted on 400 Norwegian postpartum women [8]. The authors reported that cranberry was one of the most commonly used herbs during pregnancy [8]. A herbal compendium reported that cranberry is of minimal risk during pregnancy when consumed in food quantities [19]. There are no clinical studies in the evidence-based medicine literature of cranberry being either safe or contraindicated during pregnancy.

Use and safety during lactation

| Grade | Unknown | 5 |

There are no reports in the evidence-based medicine literature of cranberry being either safe or contraindicated during lactation.

Toxicity and adverse effects

Cranberries have been consumed as a food throughout recorded history and have proven safe as a food item. This track record of safety does not necessarily imply, however, that the fruit (processed or not) is entirely safe in all populations or at high levels of consumption. One possible area of concern is patients at risk of kidney stones. In a study of healthy volunteers consuming cranberry tablets for one week at the manufactures recommended dose, urinary oxalates were found to have increased significantly [20]. While consumption of up to 4L/day of cranberry juice has been shown to be non-toxic in healthy individuals [21], people with nephrolithiasis may be at increased risk for stone formation if consuming large amounts of
cranberries or cranberry juice. In infants and young children, gastrointestinal distress, including diarrhea, has been reported when consuming more than 3L/day of cranberry juice [22-24].

**Pharmacology**

The proanthocyanidins present in cranberry fruit interfere with bacterial adherence to the urinary tract epithelial cells [25-33]. The fructose in cranberries has also been shown to contribute to the antibacterial activity of cranberry [31, 34, 35]. In the case of *Escherichia coli* (*E. coli*), the cause of most urinary tract infections, proanthocyanidins have been shown to wrap around these bacteria and prevent their adherence to the urinary tract wall [13, 34, 36, 37]. Cranberry juice cocktail was shown to inhibit adherence in 77 clinical isolates of *Escherichia coli* obtained from patients with diagnosed urinary tract infections [36]. It has been demonstrated, however, that cranberry does not appear to be able to dislodge bacteria that have already adhered to the urinary tract epithelial cells [38].

Cranberry juice has antibacterial activity against *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* [30, 34, 36]. Cranberry has been shown to have antiviral action against the poliovirus type 1 [39]. Cranberry has been found to prevent the adherence of *Helicobacter pylori* (*H. pylori*) in the stomach [12, 13]. Cranberry may also prevent adhesion of plaque bacteria that cause periodontal disease [14-16]. Recent findings indicate that cranberry may even reduce adhesion and infectivity of the influenzae virus [17]. Cranberry has significant levels of antioxidant and has demonstrated anticarcinogenic activity [40, 41].

**Drug Interactions**

Anecdotal reports of interaction with warfarin have been made [42-44], however, in a clinical study of 14 healthy individuals, no alteration of CYP2C9, the enzyme responsible for metabolizing warfarin, was evident [45]. One laboratory study indicates that cranberry juice
may inhibit enteric CYP3A4 [46], yet a clinical study found no evidence of altered levels of cyclosporine, a CYP3A4 substrate, due to consumption of cranberry juice [47].

Discussion

There is extensive research on the constituents and potential therapeutic properties of cranberry fruit and juice. The predominant theme of the research to date, both clinical and preclinical, involves the exploration of cranberry fruit’s ability to reduce the risk of infection, particularly of the urinary tract, by a process of directly inhibiting a pathogen’s ability for tissue and host cell adherence. Evidence suggests that not only is this possible for bacteria, but also for viruses as well.

There is very strong evidence supporting the use of cranberry in the prevention of urinary tract infections. A Cochrane database systematic review investigating the use of cranberry for the prevention of urinary tract infections concluded that cranberry juice may effectively prevent the frequency of urinary tract infections [11]. While evidence regarding other uses of this fruit is nowhere near as rigorous, there are some promising in vitro evidence related to oral hygiene, H. pylori induced stomach ulceration, and even possibly in the prevention of influenza.

There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. As reported above, a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of cranberry is unknown. Its common usage, low toxicity and the fact that cranberries are eaten as a food, however, does support the hypothesis of safety in pregnancy and lactation when consumed in food amounts. At higher dosages, however, the safety or harm cannot be confirmed without further high quality clinical studies.
In the situation where a woman is predisposed to nephrolithiasis, however, caution is warranted in the consumption of foods containing high amounts of oxalic acid, cranberries included. Increased risks to the fetus either from radiographic diagnosis, treatment, and even stone passage make the formation of kidney stones even more problematic and potentially risky for the pregnant woman [48]. It should be noted, however, that pregnant women are not generally at increased risk for stone formation [49].

Overall, cranberry appears to be a useful therapeutic agent for the prevention of urinary tract infections in women who are either pregnant or breastfeeding. Promising evidence regarding other anti-infective properties of cranberry need to be pursued including improved oral hygiene, stomach ulceration, and the prevention of influenza. It is encouraging that there is a nutritious natural health product available that, in most cases, may safely prevent a common and debilitating complaint in pregnant woman.

Acknowledgements

The Canadian College of Naturopathic Medicine, Motherisk – Sick Kids Hospital, University of Toronto and McMaster University
<table>
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<tr>
<th>Grade</th>
<th>Level of Evidence</th>
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<tr>
<td>A</td>
<td><strong>Very Strong Scientific Evidence</strong>&lt;br&gt;Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.</td>
</tr>
<tr>
<td>B1</td>
<td><strong>Strong Scientific Evidence</strong>&lt;br&gt;Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).</td>
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<tr>
<td>B2</td>
<td><strong>Good scientific evidence</strong>&lt;br&gt;Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.</td>
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<tr>
<td>C</td>
<td><strong>Fair Scientific Evidence</strong>&lt;br&gt;Statistically significant evidence of benefit from one or more cohort studies OR outcome studies.</td>
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<tr>
<td>D</td>
<td><strong>Weak Scientific Evidence</strong>&lt;br&gt;Evidence from case series.</td>
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<tr>
<td>E</td>
<td><strong>INDIRECT and/or Clinical evidence</strong>&lt;br&gt;Evidence from case reports OR expert opinion OR laboratory studies.</td>
</tr>
<tr>
<td>F</td>
<td><strong>Historical or traditional evidence</strong>&lt;br&gt;Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.</td>
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Table 2. Levels of evidence for harm

<table>
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<th>Level</th>
<th>Evidence</th>
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| 1a    | **Very Strong scientific evidence**  
Statistically significant evidence from one or more systematic reviews or RCTs. |
| 1b    | **Strong Scientific evidence**  
Statistically significant evidence from one or more cohort studies OR control study. |
| 1c    | **Good Scientific evidence**  
Evidence from one or more case series. |
| 2     | **Fair Scientific evidence**  
Evidence based on case reports. |
| 3     | **In vitro scientific evidence**  
Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells. |
| 4     | **Theoretical evidence**  
Evidence based on scientific theory OR expert opinion. |
| 5     | **Unknown**  
No available information. |
REFERENCES


10.2 Work performed by the student

Ed Mills, Gideon Koren and I conceptualized this project as a continuation of the work from Chapter 2. I conducted the systematic review and wrote the majority of the manuscript. Ed Mills, Dugald Seely and Dan Perri provided comment and edits depending on their various area of specialization. Gideon Koren was the senior scientist on this study.

10.3 Statement of significance and impact

Cranberry pills or juice are commonly used for the prevention of urinary tract infections. To my knowledge, this is the first systematic review to examine the safety of cranberry during pregnancy and lactation. Since urinary tract infections may occur during pregnancy, it is likely that women may seek an alternative treatment for the prevention of urinary tract infections, such as cranberry. Examining the safety of cranberry during pregnancy and lactation is clinically relevant.
11 Summary and General Discussion

The results from Chapters 3-10 will be summarized and discussed in the following sections.

11.1 Summary of conclusions from each chapter

In total, 79 NHPs were systematically reviewed as part of my dissertation (Table 11.1). Evidence of safety during pregnancy was assessed for 79 NHPs whereas for lactation, the evidence was assessed for 77 NHPs (Table 11.1). A meta-analysis on safety during pregnancy was performed on 2 NHPs (*Lactobacillus spp.* and *Bifidobacterium spp.*) (Table 11.1). Two (2) NHPs (common and cassia cinnamon) were systematically reviewed for their general clinical indications, including safety during pregnancy and lactation (Table 11.1).

In Chapter 2, I presented a new system for evaluating evidence of NHP safety during pregnancy and lactation. This system was developed through work on 75 systematic reviews of NHPs during pregnancy and lactation, which was published as a textbook\(^{22}\) (Appendix A). The system is further discussed in Section 11.3.1.

In Chapter 3, I presented the results of a systematic review and meta-analysis of randomized controlled trials (RCT) for three probiotic species, i.e. *Lactobacillus, Bifidobacterium* and *Saccharomyces* spp. The meta-analysis demonstrated that versus placebo, certain species of *Lactobacillus* and *Bifidobacterium* did not adversely impact birth weight, gestational age or incidence of C-section delivery when administered to pregnant women. The systematic review demonstrated that treatment with certain strains of *Lactobacillus* and *Bifidobacterium spp.* during pregnancy may reduce the incidence of atopic disease in newborns and may be efficacious for the treatment of BV. No RCTs were available in the scientific literature on *Saccharomyces spp.* treatments during pregnancy.

In Chapter 4, I presented the results of a systematic review on common and cassia cinnamon (*Cinnamomum verum* and *C. aromaticum*, respectively). Clinically, there are conflicting data from RCTs as to the effect on fasting glucose and blood lipid measurements in type 2 diabetics.
Thus far, no change was observed in glycosylated hemoglobin (HA1c). Both common and cassia cinnamon demonstrated low toxicity profiles, where they are considered as GRAS (Generally Regarded As Safe) by the United States Food and Drug Administration (USFDA,) and were associated with minimal adverse events, such as mucosal and skin irritation at high doses. Common and cassia cinnamon were investigated as a preliminarily step towards assessing if these NHPs could be of further study as a treatment for gestational diabetes.

In Chapter 5, I presented the results of a systematic review of St. John’s wort (*Hypericum perforatum*) during pregnancy and lactation. Although there is conflicting data on the efficacy of St. John’s wort for the treatment of mild to moderate depression, it is a commonly used and prescribed NHP. In cases were pregnant women seek an alternative to anti-depressant drugs, they would likely gravitate towards St. John’s wort. At the time of this systematic review, the only clinical evidence of St. John’s wort use during pregnancy was a case report. Since this systematic review, Moretti et al. (2009) conducted a cohort study on 54 pregnancies exposed to St. John’s wort and found no evidence of increased risk of major or minor malformations

In Chapter 6, I presented the results of a systematic review of gingko (*Ginkgo biloba*) during pregnancy and lactation. Ginkgo is a popular herb used for memory and cognitive function, despite conflicting evidence of efficacy. The safety of ginkgo in pregnancy and lactation is unclear as there were no data related to its use during pregnancy and lactation. Since anti-platelet activity has been demonstrated *in vitro*, ginkgo should be taken with caution, particularly around the time of delivery.

In Chapter 7, I presented the results of a systematic review of black cohosh (*Actea (Cimicifuga) recemosa*) during pregnancy and lactation. There is clinical evidence for the treatment of menopausal symptoms and arthritis (in combination with other herbs) with black cohosh. A survey of midwives in the United States found that 45% of midwives use black cohosh to induce labour. Black cohosh is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called *partus preparatus*. In addition to black cohosh, *partus preparatus* may include *Mitchella repens, Viburnum prunifolium, Caulophyllum thalactroides, Aralia nudicaulis, Leonurus cardiaca, Nepeta cataria, Rubus idaeus and Gelsemium sempervirens*. In pregnancy, there was theoretical and expert opinion evidence of the following: 1) labour-inducing effects, 2) hormonal
effects, 3) emmenagogue properties and 4) anovulatory effects. In lactation, there was theoretical and expert opinion evidence of hormonal effects.

In Chapter 8, I presented the results of a systematic review of blue cohosh (*Caulophyllum thalactroides*) during pregnancy and lactation. According to a survey of midwives in the United States, approximately 64% of midwives reported using blue cohosh as a labour-inducing aid. Blue cohosh is commonly used as part of *partus preparatus*, discussed in the paragraph above. There were three cases reports of adverse effects associated with blue cohosh: 1) perinatal stroke, 2) acute myocardial infarction, profound congestive heart failure and shock, 3) severe multi-organ hypoxic injury, and 4) abortifacient activity. In the case report of perinatal stroke, a causal relationship was unclear due to the confounding presence of benzoylgonine, a cocaine metabolite, in urine and meconium samples. In their correspondence with the editor, the authors of this case appeared to have ruled out cocaine use by the mother and adulteration of the blue cohosh product used; rather, they attributed their findings to a laboratory instrument or analysis error, which is being further investigated. In the remaining cases, it appeared that the adverse effects were associated with non-medically supervised use of blue cohosh. Blue cohosh also demonstrated teratogenic, embryotoxic and oxytocic effects via *in vitro* evidence.

In Chapter 9, I presented the results of a systematic review of chastetree (*Vitex agnus-castus*). There is clinical evidence for the treatment of premenstrual syndrome (PMS) and cystic mastalgia with chastetree. Women with PMS and cystic mastalgia may be unknowingly pregnant while undergoing treatment with chastetree. Unfortunately, the evidence of safety for chastetree is limited to expert opinion and scientific theory.

In chapter 10, I presented the results of a systematic review of cranberry (*Vaccinium macrocarpon*). Cranberry is used for the prevention of urinary tract infections (UTIs). Since urinary tract infections may occur during pregnancy, it is likely that women may seek an alternative treatment for the prevention of urinary tract infections, such as cranberry. Based on a survey of pregnant women who reported no adverse effect associated with cranberry intake, there appears to be evidence of minimal risk associated with cranberry during pregnancy.

In Appendix A, I presented the 75 systematic reviews from the textbook I co-wrote with Doctors Mills, Perri and Koren in monograph format: common name, latin name, synonyms, indications, pregnancy, lactation, contraindications, caution, constituents, toxicity, pharmacology, drug
indications and parts used. I am the second author on the manuscript detailing the genesis of the MotherNature Network, i.e. a network of medical and complementary and alternative medicine (CAM) practitioners, researchers and scientists, which is further discussed in Section 11.3.4. There are two systematic review manuscripts, i.e. ginseng and Echinacea, where I conducted the majority of the work but am listed as the second author. As such, these reviews are not discussed in detail in this thesis.

In Appendix B, I presented two meta-analyses conducted on traditional Chinese medicine treatments for liver and lung cancer. Since these studies are not appropriate for the theme of this dissertation, they will not be discussed further.

11.2 Status of the various working hypotheses

The objective of this dissertation was to review the present state of evidence on the safety of NHPs during pregnancy and lactation, and to create a new system to validate evidence on NHPs during pregnancy and lactation designed to affect medical decision. The new system of evaluating evidence of NHP safety in pregnancy and lactation is discussed in Section 11.3.1. The working hypotheses were: 1) there is evidence of safety associated with the use of NHPs during pregnancy, 2) there is evidence of safety associated with the use of NHPs during lactation and 3) there is evidence of effective NHP interventions for high-risk pregnancies.

In most cases, there were data on NHP safety during pregnancy. Only 7 NHPs did not have safety data during pregnancy (Table 11.2). Despite the presence of data, the quality of data is a completely different issue. The vast majority of evidence on safety was based on theory, expert opinion, in vitro studies or animal studies (Tables 11.3). At first glance it would appear that there were a large number of clinical trials of NHPs during pregnancy (Table 11.3). If vitamins are excluded from this list, whereby vitamins have historically been studied in pregnancy for pre-natal supplementation, the extent of clinical data is considerably diminished (Table 11.3). There were even less safety data on NHP use during lactation (Table 11.4). Of the NHPs systematically reviewed, no evidence could be found on safety during lactation for 24 NHPs (Table 11.2). NHP use in pregnancy is generally regarded as being poorly studied. Based on the data of this dissertation, NHP evidence of safety during lactation is even scarcer.
Working hypotheses #1 and #2 of this dissertation aimed at ascertaining the presence of evidence on NHP safety during pregnancy and lactation, respectively. Based on the evidence uncovered in this dissertation, I can conclude that these two hypotheses were proven for a number of NHPs studied in pregnancy and lactation, but not for all the NHPs studied; in pregnancy, hypotheses #1 was proven for 72 NHPs, but unproven for 7 NHPs; in lactation, hypotheses #2 was proven for 53 NHPs, but unproven for 24 NHPs.

With respect to hypothesis #3, the identification of two herbs (cassia and common cinnamon) that are effective and of therapeutic benefit to high-risk pregnancies, this hypothesis was not proven or disproven in this dissertation due to the small sample size analyzed. Common and cassia cinnamon were investigated for their use in diabetes and in particular, gestational diabetes; however, there were no data (clinical, in vitro or other) on their use in pregnancy or lactation. Despite the absence of data on common and cassia cinnamon, these should be further studied in gestational diabetes given the clinical evidence of efficacy of cassia cinnamon in type 2 diabetes, even though conflicting, and the low toxicity profile. The next step would be to evaluate if common and cassia cinnamon cross the placenta via an ex vivo human placenta model. Should common or cassia cinnamon show low levels or absence of perfusion through the placenta, they could be further studied via a prospective cohort or RCT as a treatment for gestational diabetes.

11.3 Overall significance of work

11.3.1 New levels of evidence for evaluating NHP safety in pregnancy and lactation

In 1992, the Evidence-Based Medicine Working Group (EBMWG) began a series of articles in the Journal of the American Medical Association (JAMA) on a new paradigm for the practice of medicine\textsuperscript{52}. The purpose of the EBMWG was to de-emphasize intuition, unsystematic clinical experience and pathophysiologic rationale as sufficient grounds for clinical decision making and to stress the examination of evidence from clinical research, this was coined evidence-based medicine (EBM)\textsuperscript{52}. The EBMWG provided clinicians with instructions on how to access, evaluate and interpret the medical literature\textsuperscript{53}. Clinicians were able to apply the principles of clinical epidemiology to day-to-day clinical practice through critical appraisal of the medical literature and the application of rigorous methodological criteria\textsuperscript{54}. 
As EBM evolved, there began a need to differentiate weak versus strong evidence. Although the Canadian Task Force on the Periodic Health Examination was one of the first efforts to classify and create a grading system based on strength of evidence, it was the EBMWG who are responsible for the genesis of evidence scales in medicine. With advances in clinical epidemiology, the EBMWG established the Grades of Recommendations for a Specified Level of Baseline Risk which consisted of a hierarchical scale with the RCTs at the top followed by poorer quality RCTs and observational studies at the bottom. Evidence scales evolved as EBM worked toward interpreting individual clinical expertise with the best available external clinical evidence from systematic research. Researchers from the EBMWG continued their work at the Oxford Center for Evidence-Based Medicine (OCEBM). The OCEBM established more recent levels of hierarchy in EBM, which were used in this dissertation and are presented in Table 11.5.

In order to develop a new system to validate evidence on NHP safety during pregnancy and lactation, a scale needed to be created. I used the OCEBM scale (Table 11.5) as a template for the proposed evidence levels of NHP safety in pregnancy and lactation. Creating a scale in pregnancy and lactation had unique challenges because it is a safety scale. At what evidence level would clinicians agree that a NHP should or should not be administered in pregnancy and lactation? Creating a scale related to NHPs also has its challenges, particularly in the case of herbs. There is tension between clinicians who have been using herbs for centuries in food, teas and medicines, and researchers requiring scientific validation of safety and efficacy. It is difficult to study the safety of herbs using large scale RCTs due to ethical issues and costs. Herbs are complex and difficult to study for the following reasons: they contain many phytochemicals, the active ingredient is often unknown, the therapeutic effect varies depending on the part used (root, stem, leaf, bark, etc.), the dosing and dosage form (capsule, tea, tincture, etc.) vary and other methodological challenges. The scale needed to provide clinicians with an easily accessible and understandable system so that they can differentiate clinical data versus evidence from in vitro data or physiological rationale. A NHP scale also posed a unique challenge in that the evidence on NHPs, particularly herbal medicines in pregnancy and lactation, is perceived to be poor. The scale had to identify different levels of robustness and not “embellish” poor evidence because of a knowledge gap. An argument could be made that other scales could have been chosen as a template, such as the US preventative Task Force ranking,
the United Kingdom (UK) National Health Service categories\textsuperscript{60} or the GRADE working group system\textsuperscript{61}. With the exception of the GRADE system, the other two scales have similarities with the OCEM scale. The OCEBM scale was chosen because it is an accepted scale in EBM, it evolved from the work of the EBMWG and because of its extensive range of study types sorted in hierarchy. In the OCEBM model, the highest level of evidence is the systematic review and meta-analysis (Level 1a) of RCTs, while the lowest level is expert opinion and scientific theory (Level 5) (Table 11.5).

If I were to apply the OCEBM model to the studies extracted as part of this dissertation, many studies would not be ranked. The new levels of evidence developed in this thesis for evaluating harm and safety during pregnancy and lactation are presented in Table 11.6. Given the large knowledge gap on NHP safety in pregnancy and lactation, I modified the hierarchy for evaluating evidence of NHP safety in pregnancy and lactation. Studies with human data were given a higher level of evidence in the proposed pregnancy scale versus the OCEBM scale as they represented evidence of clinical experience (Table 11.6). This has limitations, however, as the power to truly detect a hazard in a small sample may not accurately be reflected in a small study. Studies with pre-clinical (\textit{in vitro} data) were given a higher level of evidence in the proposed scale versus the OCEBM scale as they represented evidence of physiologic rationale (Table 11.6). This has limitations, however, as pre-clinical evidence does not always translate into safety and efficacy in clinical studies.

In this dissertation, I evaluated the level of evidence for each study extracted in the systematic review; the highest level of evidence for a NHP in pregnancy is presented in Table 11.3 and the highest level of evidence for a NHP in lactation is presented in Table 11.4. When examining Tables 11.3 and 11.4, it is clear that the evidence in pregnancy and lactation for the vast majority of NHPs studied is classified under Level 4 or Level 5, which are the lowest forms of evidence.

I proposed the highest level of evidence in pregnancy and lactation as “Level 1a”, which represents RCTs, systematic reviews and meta-analyses (Table 11.6). Although in evidence-based medicine the highest level of evidence is typically regarded as the systematic review and meta-analysis of RCTs, as seen in the OCEBM model, I proposed that a RCT conducted in pregnancy or lactation was equal in hierarchy to the systematic review and meta-analysis. The existence of RCTs in pregnancy and lactation research is uncommon, especially more so if the
RCT is conducted on a NHP. The knowledge gap of NHP safety in pregnancy and lactation is so large that evidence originating from a RCT could have an enormous impact on medical decision. The inclusion of the RCT as “Level 1a” evidence could provide health care practitioners with a strong level of comfort that the NHP associated with this level had strong clinical evidence of safety in pregnancy or lactation. When examining the data of this dissertation, 20 NHPs had Level 1a evidence in pregnancy (Table 11.3) and 8 NHPs has Level 1a evidence in lactation (Table 11.4).

Although the RCT and systematic review/meta-analysis of RCTs are at the top of the hierarchy in the proposed model, there are some limitations and criticisms of these types of studies. 1) There is a publication bias in the literature towards positive RCTs. Published studies in medical journals may not be representative of all the studies that are completed on a given topic and may be misleading due to conflicts of interest and failure to publish negative studies. Many medical journals now require RCTs to be registered at their onset in order for them to be published. 2) RCTs are costly. 3) In rare diseases, the number of participants is limited for a RCT. 4) In some cases, it may not be ethical to conduct a RCT and an observational study may be more appropriate. 5) There are issues of generalizability associated with RCTs where it may not be possible to extrapolate results to different populations and for longer time frames; questions always remain about how far and to which populations the results are "generalizable. Limitations in inclusion and exclusion criteria also limit the generalizability of the results. 6) In a RCT, there is conflict between results observed in a “controlled” environment versus “real life”. 7) RCTs due to their short-term focus may miss medium-term and long-term side effects. As such, pertinent safety information may be absent.

In the pregnant population, there are limitations and criticisms associated with RCTs: 1) the fetus cannot consent to the study, 2) it is unethical to investigate harm in pregnant women, e.g. teratogenic risk, abortifacient effects or adverse effects, 3) the potential risks of participating in the RCT to the mother, fetus, newborn and mother’s fertility may not be known, 4) in cases of pregnancy-related complications, the mother and fetus could be harmed by being randomized to the placebo group and not receiving treatment, and 5) in cases of addiction or pharmacologic effect to both mother and fetus, replacing care with a placebo could lead to adverse effects.
NHPs without any evidence in pregnancy and lactation were assigned as “Level 5” (Table 11.6). Throughout the reviews, 7 NHPs had no evidence of safety in pregnancy while 24 NHPs had no evidence of safety in lactation (Table 11.2). In the OCEBM scale, there is no level assigned to “unknown” evidence. I proposed that there needed to be a level designated for unknown information in order for researchers and funding agencies to clearly identify the large knowledge gap in this area; researchers could plan future research projects and funding resources could be allocated accordingly.

When evidence was available, a large number of studies involved scientific theory or expert opinion as the main basis for describing the safety of a NHP during pregnancy and lactation (Tables 11.3 and 11.4). According to the OCEBM, this type of evidence is considered the lowest level of evidence (Level 5 in Table 11.5). In my model, expert opinion and scientific theory evidence was proposed as “Level 4” evidence in order to highlight that 1) the NHP safety was not unknown and 2) the NHP has at least been examined for potential safety during pregnancy and lactation based on a rationale of expert opinion or scientific theory, even though the examination was neither pre-clinical nor clinical in nature (Table 11.6). Throughout the reviews, 15 NHPs had Level 4 evidence in both pregnancy and lactation (Tables 11.3 and 11.4).

Level 3 was another level of evidence in pregnancy and lactation that was seen in large numbers in this dissertation (Tables 11.3 and 11.4). Level 3 corresponds to in vitro evidence based on scientific studies conducted on animals, insects or microorganisms, and laboratory studies on human cells or tissue (Table 11.6). In the OCEBM model, there is no evidence level assigned to in vitro studies (Table 11.5). The inclusion of in vitro studies in the pregnancy and lactation hierarchy of evidence scale was designed to emphasize the importance of studies on NHPs in pregnancy or lactation that had pre-clinical data, although these data were a lower form of evidence they do represent evidence of physiologic rationale. It is difficult to extrapolate in vitro studies to humans. In some cases, NHPs or drugs are administered to animals at extremely high doses, well above standard therapeutic doses. At first glance, this would appear to over-exaggerate a therapeutic response or adverse effect. The dosing rationale does reflect an assumption that the dose given to the animal correlates to the dose in a human; however, it is never known for certain. Applying the results of in vitro evidence clinically has its challenges. Animal study data provides valuable pre-clinical data from which researchers can design clinical studies. The same intervention in an animal may have a beneficial effect, no effect or cause
adverse effects in a human; the outcome is never certain until it is clinically studied. In pregnancy, an argument could be made that in vitro evidence of harm should be sufficient to discourage clinicians from recommending the intervention. What if the benefit outweighed the harm and a treatment is performed with the patient’s consent? Garlic and ginger are examples where there was in vitro evidence of harm and clinical evidence of safety and therapeutic benefit (Appendix A). A Research Ethics Board (REB) would evaluate the potential of harm on a case-by-case basis before a drug or NHP intervention would be approved for clinical study. In lactation, the risk of applying in vitro evidence clinically may appear less severe at first glance. The cases of newborn morbidity and death previously discussed\(^49,50\) should discourage such an assumption, particularly in the area of lactation where the evidence of NHP safety is poorer than pregnancy. Throughout the reviews, 22 NHPs had Level 3 evidence in both pregnancy and lactation (Tables 11.3 and 11.4).

With respect to the lowest evidence-based form of clinical data, i.e. a case report, the OCEBM does not list case reports in their hierarchy of evidence (Table 11.5) whereas in the pregnancy and lactation scale in this dissertation, case reports were proposed as “Level 2” evidence (Table 11.6). Given that well over half of the evidence uncovered in this thesis on pregnancy and lactation was poor, i.e. pre-clinical, expert opinion or scientific theory-based, or unknown (Tables 11.3 and 11.4), clinical safety data needed to be emphasized in the scale as it could affect medical decision. There are a number of limitations with case reports, such as 1) uncertainty if intervention is the causative factor, 2) there is no denominator to assess the rate, 3) uncertainty if outcome is a common event, 4) bias towards abnormal outcomes, 5) information is often incomplete, 6) bias towards positive outcomes or adverse events, and many other limitations. Case reports on herbs also have limitations: 1) the product is not always tested for contamination or adulteration, 2) it may not be known what specific herb is in the bottle (correct genus and species, correct medicinal part used, correct preparation), 3) the dosing may be outside of therapeutic range, 4) poor reporting and other limitations. In pregnancy and lactation, the main strength of a case report is that it is clinical data of safety, harm or therapeutic benefit; the main weakness it is only one case and the outcome may not be representative of safety, harm or therapeutic benefit. Throughout the reviews, 5 NHPs had Level 2 evidence in pregnancy and 1 NHP had Level 2 evidence in lactation (Tables 11.3 and 11.4).
With respect to case series and cohort studies, the OCEBM model considers these as Level 4 evidence and Level 2 evidence, respectively (Table 11.5). Given the poor clinical data extracted throughout the systematic reviews, the presence of any clinical data in case series or cohort format is important evidence in pregnancy and lactation research and may affect medical decision. As such, case series were assigned as “Level 1c” evidence and cohort studies were assigned as “Level 1b” evidence (Table 11.6). In some cases, observational cohort studies show similar results to the RCT. Due to a lack of randomization and placebo, it is not known for certain that the observed outcome is not from chance. A cohort study does present a favorable methodological solution for clinical research in pregnancy and lactation: it allows the researcher to study women that are already undertaking a treatment, without exposing them to a new intervention (treatment arm of the RCT) or discontinuing treatment (placebo arm of the RCT). Many of the NHP studies from the Motherisk Program, e.g. Echinacea and St. John’s wort (Appendix A and B; Section 11.1), were studied using a cohort method. Throughout the reviews, 1 NHP had Level 1c evidence in both pregnancy and lactation, and 9 NHPs had Level 1b evidence in pregnancy and 6 NHPs had Level 1b in lactation (Tables 11.3 and 11.4).

The model proposed in this dissertation presents the existing evidence on NHP safety in a format that reflects the knowledge gap and generally poor data quality in this area of research. It also allows health care practitioners to make sense and qualify evidence when decisions on patient care are required that involve NHPs. Although this model is based on 79 systematic reviews, it requires further validation and should be applied to other NHPs in pregnancy and lactation.

11.3.2 Harmful NHPs in pregnancy

When looking at the list of NHPs studied as part of this dissertation, it is not surprising that there were safety concerns associated with herbal medicines with narrow therapeutic ranges and known toxicity or herbal medicines from which pharmaceutical drugs are extracted. These herbal medicines were:

- deadly nightshade (*Atropa belladonna*) from which is derived atropine\(^1\),
- ephedra (*Ephedra spp.*) from which is extracted ephedrine\(^1\),
– foxglove (*Digitalis lanata* and *D. purpurea*) from which is extracted digitoxin and digoxin,

– calamus (*Acorus calamus*) which contains the potentially carcinogenic compound beta-asarone, and

– juniper (*Juniperus communis*) which contains the potential abortifacient isocupressic acid.

Of most concern, however, is blue cohosh (*Caulophyllum thalictroides*). There were 3 case reports that blue cohosh taken at the time of delivery may cause 1) perinatal stroke, 2) acute myocardial infarction, profound congestive heart failure and shock, and 3) severe multi-organ hypoxic injury (Chapter 8). Although a causative relationship was unclear with respect to the perinatal stroke case and the authors withdrew some of the conclusions of their report due to potential adulterants or sample contamination (Chapter 8), it is plausible blue cohosh could cause cardiovascular birth defects due to its vasoconstrictive effect on coronary vessels. In the US, 64% of surveyed midwives reported using blue cohosh to induce labour, however, they reported that blue cohosh was the herbal medicine used in pregnancy with the lowest comfort level.

In the 3 case reports above, the patients taking blue cohosh were not closely monitored and may have exceeded the therapeutic window of this herbal medicine. Given the potential risk for harm when used outside of its therapeutic window, the blue cohosh administration should be restricted to medical professionals trained in its administration at delivery, such as obstetricians, midwives, naturopathic doctors and medical herbalists. As NHPs are frequently unregulated, governmental agencies should take immediate steps to limit public access to blue cohosh in order to prevent the administration of this herb without the supervision of a licensed and trained medical professional. In Canada, blue cohosh should be added to Schedule F of the Food and Drug Regulations. Schedule F is a list of medicinal ingredients which, when present in a drug, require the drug to be sold only pursuant to a verbal or written prescription.

There were safety concerns associated with known abortifacients, i.e. pennyroyal (*Mentha pulegium*) and parsley (*Petroselinum crispum* and *P. sativum*). Pennyroyal has a long tradition of use as an abortifacient and has been documented in case reports as inducing abortion.
Parsley is documented in traditional texts as an abortifacient and was reported as being frequently used to induce abortions at the Montivideo Poison Center, Uruguay\textsuperscript{68}.

Berberine-containing herbal medicines, such as barberry (\textit{Berberis vulgaris}), goldenseal (\textit{Hydrastis canadensis}) and Oregon gape (\textit{Berberis aquifolium}), were of potential safety concern around the time of delivery. Berberine displaces bilirubin bound to albumin and therefore, may aggravate newborn jaundice\textsuperscript{69}.

Of the remaining herbal medicines studied, many should be used with caution or simply avoided until there is evidence to support safe use in pregnancy.

11.3.3 Apparent safe and potentially effective NHPs in pregnancy

Of the NHPs studied in this thesis, some NHPs had evidence to support their use with apparent safety and others may have therapeutic benefit when taken during pregnancy. These are discussed below.

- Cranberry was reported as being commonly used by pregnant women in Norway to treat urinary tract infections (Chapter 10).

- Echinacea was used by 206 women during pregnancy, including women who had used echinacea in the first trimester, without an increased risk of malformations. Echinacea is commonly used to treat upper respiratory tract infections (Appendix A).

- Garlic was used to treat women with pre-eclampsia without adverse outcome to the pregnancy (Appendix A). Although the pre-eclampsia study showed no difference between the garlic and placebo group, garlic has other therapeutic indications, such as hypertension, hypercholesterolemia, upper respiratory tract infection and others, that may be of benefit during pregnancy (Appendix A).

- Ginger and vitamin B6 were shown to be effective treatments for morning sickness without adverse outcome to the pregnancy (Appendix A).
– Horsechestnut seed extract was shown to be of therapeutic benefit to women with pregnancy-induced venous insufficiency without adverse outcome to the pregnancy (Appendix A).

– Korean ginseng was shown to be of therapeutic benefit for the treatment of intrauterine growth retardation without adverse outcome to the pregnancy (Appendix A).

– Milk thistle was shown to have no adverse effect on pregnancy outcome when taken by pregnant women for minor liver insufficiencies (Appendix A).

– Peppermint was shown to be of benefit for the treatment of pregnancy-induced nausea, but there were no data on pregnancy outcome following its administration (Appendix A).

– When taken at 32 weeks gestation, raspberry leaves were shown to shorten the second stage of labour and lower the rate of forceps delivery when compared to placebo (Appendix A). No adverse pregnancy outcome was reported with the use of raspberry.

– When taken during the second and third trimester, senna did not have a negative effect on gestational age at delivery, birth weight or incidence of malformations. Senna also demonstrated therapeutic benefit for the treatment of pregnancy-induced constipation.

– As discussed in section 11.1 and Chapter 5, St. John’s wort was shown not to increase the risk of malformations when taken during pregnancy. St. John’s wort is commonly used to treat mild to moderate depression.

– Fish oils were shown to have no negative outcome on pregnancy and have many therapeutic benefits, such as increased cerebral maturation of newborns, improved post-natal oxidative stress, reduced expression of atopic disease, and improved mental processing and IQ (Appendix A).

– Strains of Lactobacillus spp. and Bifidobacterium spp. were shown not to affect gestational age, birth weight, incidence of C-section or risk of malformations (Chapter 2). LGG, L. reuteri, L. rhamnosus, B. breve and Propionibacterium freudenreichii where shown to reduce the incidence of atopic disease in newborns when taken during pregnancy and lactation (Chapter 2). When taken during pregnancy, B. lactis was shown to affect the placental fatty acid transfer from mother to fetus (Chapter 2).
With the exception of vitamin A where there is conflicting evidence on the maximal daily dose to avoid malformations, vitamins D, E, K, B6 and folic acid did not have a negative effect on pregnancy outcome, rather these vitamins were necessary for a healthy pregnancy (Appendix A).

11.3.4 Apparent safe and potentially effective NHPs in lactation

A number of NHPs studied demonstrated apparent safety and therapeutic benefit when taken during lactation. These are outlined below.

- Borage oil was administered to breastfeeding women with no reports of adverse effects. Borage oil was shown to increase the gamma linolenic acid content of breast milk (Appendix A).

- Evening primrose oil was administered to women between the second and sixth month of lactation without any reports of adverse effects. Evening primrose oil was shown to increase the long chain polyunsaturated fatty acid content of breast milk when taken along with fish oils (Appendix A).

- Garlic was shown to have no effect on the number of times a newborn fed nor the amount of milk they consumed when taken by the mother during breastfeeding (Appendix A). Although no adverse effects were reported with the use of garlic during lactation, short-term behavioural changes were observed in the newborns as mothers enrolled in one study went from the placebo to garlic supplementation (Appendix A).

- Senna was shown to be effective at treating constipation immediately post-partum. Senna was well tolerated with abdominal cramps occurring in 13% of mothers and no adverse effects on lactation (Appendix A).

- *LGG, L. reuteri, L. rhamnosus, B. breve* and *Propionibacterium freudenreichii* where shown to reduce the incidence of atopic disease in newborns when taken during pregnancy and lactation (Chapter 2).
– Vitamins A, D, E, K, B6 and folic acid did not have a negative effect on lactation, rather were necessary to support healthy lactation (Appendix A). In the case of patients infected with the human immunodeficiency virus (HIV), there is conflicting evidence regarding the use of vitamin A during lactation where vitamin A may increase the risk of vertical transmission of the HIV virus (Appendix A).

According to traditional medicine texts, fenugreek is the most commonly recommended herbal medicine to promote lactation in breastfeeding women. Unfortunately, no safety data were available for its use during lactation.

11.3.5 Limitations

In most research projects, there are limitations. The limitations associated with my dissertation are listed below.

– There was a single reviewer for most of the systematic reviews (this author) and two reviewers for the meta-analysis. As such, there is a potential risk of bias.

– Not all NHPs were systematically reviewed. The amino acids, minerals, supplements, Chinese patents and other herbal medicines were not investigated as part of my dissertation. Although the most commonly used NHPs were selected, including commonly used NHPs in pregnancy, lactation and women’s health, other NHPs should be investigated for safety in pregnancy and lactation.

– A number of databases were searched as part of this dissertation, but new databases have emerged that should be searched in future reviews. These databases include Reprotox (Micromedex), Toxline, Napralert, CAB abstracts, MedWatch, WHO and Chinese databases (CNKI and Wan Fang). EMBASE was added in later reviews (Section 3), but not in the earlier systematic reviews. EMBASE should be included in the list of searched databases moving forward.

– There are different preparations of a NHP (essential oil, alcoholic extract, tea, capsule and others). Wherever apparent safety or potential harm was discussed, I endeavored to list the type of preparation for the NHP reviewed. Given the scarcity of data, it cannot be assumed
that other preparation types of the NHP are either safe or potentially harmful in pregnancy and lactation.

- There is a timeline in pregnancy, i.e. preconception, 1st, 2nd, and 3rd trimesters, labor and delivery. An intervention during organogenesis is more likely to cause birth defects versus an intervention outside of this period. An intervention that may cause a miscarriage is more likely to be an issue in the first to second trimester. Different NHPs will have different effects based on timing, dose, mechanism of action and product formulation on the development of the fetus and stage of pregnancy. In my dissertation, NHP safety was defined as “apparent safety” where I endeavored to associate as much detail as possible for the clinician so that they may make an informed decision. For example, Echinacea was studied throughout pregnancy (Appendix B) in comparison to red raspberry, which was studied from 32 weeks of gestation onwards (Appendix A).

- Data in the systematic reviews were not extracted from reference books (secondary sources) as part of the methodology. In keeping with evidence-based principles, primary information from the scientific literature was the main focus throughout the searches. Some reference books were consulted; principally for herbal toxicology, but an argument could be made that traditional herbal and traditional Chinese medicine textbooks may have data related to pregnancy and lactation. These data, however, would have a low rating on the evidence scale proposed in this dissertation.

- Homeopathic preparations of some of the herbal medicines were discussed in the systematic reviews. These studies were extracted because homeopathic preparations are often named after the Latin name of the herb, e.g. St. John’s wort is known as homeopathic hypericum. Homeopathic preparations use minute doses of herbal medicines following successive dilution and are a completely different system of medicine in comparison to herbs, vitamins, minerals and supplements. The results in this dissertation do not represent a systematic review of homeopathy safety in pregnancy and lactation.
11.3.6 Future areas of research

During the course of my PhD, I was involved in the creation of the MotherNature Network of the Sick Kids Hospital Motherisk Program. Through a series of workshops, the MotherNature Network was created to form longstanding research collaborations amongst Canadian medical and CAM practitioners, researchers and scientists. The details of the MotherNature workshop were published in 2008 and are presented in Appendix B.

Through work conducted as part of this dissertation and feedback from the MotherNature Network, a number of proposed studies were conceived in order to improve the knowledge gap in this area of research. The studies discussed below are my blueprint for change in the field of NHP safety in pregnancy and lactation.

*Midwife Survey and prospective cohort*

According to a survey of midwives in the United States, between 45% to 93% of midwives will prescribe some form of NHP to women during their pregnancy. Based on the prevalence of NHP prescriptions by midwives in the United States, a similar survey of midwives in Canada would provide invaluable data on NHP use in pregnancy and lactation by Canadians.

Midwife clinical observations could fill many of the knowledge gaps on NHP safety in pregnancy, particularly around the used of herbal medicines to induce labour. Since Canadian midwives are regulated health professionals in the majority of provinces and territories (British Columbia, Alberta, Manitoba, Ontario, Quebec, Northwest Territories, Saskatchewan (pending) and Nova Scotia (pending)), they are obligated to maintain detailed patient files. It is assumed that midwives would record in the charts if their patients had consumed NHPs or been prescribed NHPs during their pregnancy, and would also chart the birth outcome. With this charted information, the safety of a NHP could be determined prospectively. If there are sufficient cases to review, it could even be argued that NHP safety could be assessed retrospectively. I believe it is essential to survey midwives in Canada, as they possess critical evidence of NHP safety in pregnancy in the files of their private practice.

The rationale for this survey is as follows: if midwives tend to recommend NHPs more frequently to pregnant and lactating women then other health professionals, surveying this group of health care professionals should provide an approximation of NHP use by Canadian women. The
primary objective would be to survey midwives across Canada to determine the prevalence of NHP use during pregnancy and lactation, including NHPs used, dosing, reported efficacy and adverse effect reporting. The secondary objective would be to identify midwife practices in Canada where patients frequently use NHPs in order to recruit research subjects for future prospective cohort studies.

The methodology would involve identifying midwives in Canada via the Canadian Association of Midwives. Midwives would be contacted via email to request that they complete an online survey. The survey would inquire about the use of NHPs in their practice. If the midwives report use of NHPs, then more specific questions would be asked pertaining to the following NHPs more commonly used in pregnancy: ginger (Zingiber officinalis), evening primrose (Oenothera biennis), raspberry (Rubus idaeus), blue cohosh (Caulophyllum thalictroides), black cohosh (Cimicifuga racemosa), squaw vine (Mitchella ripens), false unicorn (Chamalerium luteum), crampbark (Viburnum prunifolium), fenugreek (Trigonella foenum-graecum) and castor oil (Ricinus communis).

Ex vivo myometrium study on herbal uterotonics and labour aids

There are a number NHPs used by women in the third trimester or closer to the time of delivery to stimulate labour. The NHPs used, reported as “labour aids” or “uterotonics”, are most often herbal medicines with the intended action to induce labour, increase the rate of contraction, “strengthen the uterus” or ripen the cervix. Unfortunately, evidence of efficacy is lacking for these NHPs. The most common herbal medicines given as uterine stimulating and labour aids are: black cohosh (Cimicifuga racemosa), blue cohosh (Caulophyllum thalictroides), castor oil (Ricinus communis), false unicorn (Chamaelirium luteum), raspberry (Rubus idaeus), squaw vine (Mitchella ripens), crampbark (Viburnum opulus), evening primrose (Oenothera biennis) and chastetree (Vitex agnus-castus).

This study would test the hypothesis that the reported uterine-stimulating and labour-aid herbal medicines listed above act directly on human pregnant myometrium to modulate its contractility in a manner compatible with a salutatory effect on the progress of labor. NHPs would be tested individually even though most are likely to have multiple chemical components. Therefore, the aims of the study would be to ask the following questions:
• Do the NHPs affect the normal spontaneous contractility of human isolated uterus?
• Can the NHPs stimulate contractions in uterine strips that are flaccid?
• Can the NHPs resolve spasmic contractions of human isolated uterus?
• Do the NHPs affect concentration-effect curves to uterine stimulants or relaxants?

Pregnant myometrium would be obtained after written consent from pregnant women at term who will undergo C-section delivery and who were not in labour. During such operations, excess tissue is dissected and routinely discarded. Hence, the study does not involve any extra risk to the mother. Myometrium samples would be collected from participants based on the inclusion and exclusion criteria below.

Inclusion: pregnant women, aged 18-45, over 37 weeks gestation, non-labouring, non-multiple pregnancy (twins, triplets, etc.).

Exclusion: non-pregnant women, aged <18 or > 45, below 37 weeks gestation, labouring, multiple pregnancy, women with major complications of pregnancy (including pre-eclampsia, hypertension, diabetes (gestational or mellitus), and premature labour), women treated with medication that may affect the myometrium.

Myometrium strips would be separated from both the endometrium and connective tissue with a scalpel and immediately processed for contractile experiments. It is estimated that 6 to 8 strips can be obtained from a single donor, which allows for each donor to act as their own control. Strips would be placed in a bath and contractility would be assessed using standard isometric recording techniques and equipment. Spontaneous activity of each sample would be monitored and the following parameters would be recorded: maximum force, minimum force, integrated area and frequency. NHPs would then be added to the myometrium bath and the measurements would be repeated. Statistically, contractility pre-NHP (control) and post-NHP would be compared in order to determine uterine stimulating activity.

*Canadian Perinatal Network survey*

The Canadian Perinatal Network is conducting a National study on the etiologies of preterm labor. A list of NHPs claimed to be emmenagogues and uterotonics has been included in this
study. The results obtained from this national study could provide the MotherNature Network with data on the most commonly used NHPs by pregnant Canadians. The data may indicate associations between NHP intake by the mother and preterm labour. However, the risks of preterm labour are multiple, including bacterial vaginosis, smoking, alcohol and substance abuse among others. Drawing a direct causal relationship between NHP use and preterm delivery is not possible from such a reporting system, but results from the national study may highlight future studies to determine causal relationships, if any.

*Mount Sinai Hospital case-control study*

The Motherisk Program will commence a case-control study at Mount Sinai Hospital to investigate use of NHPs among women hospitalized for premature contractions, as compared to a control group that is hospitalized to give birth at term. As discussed above in the Canadian Perinatal Network National Study, the Mount Sinai study poses the same challenges in interpreting results.

*Quebec Pregnancy Registry nested case control study for fetal malformations*

The Quebec Pregnancy Registry includes data from three administrative databases in the Province of Quebec: la Régie de l’Assurance Maladie du Québec (RAMQ), Med-Écho and Le fichier des événements démographiques du Québec (birth and death registries) of l’Institut de la Statistique du Québec (ISQ). The RAMQ database contains information on medical services received by all Quebec residents and all diagnoses are classified according to the International Classification of Diseases, Ninth revision (ICD-9). The Med-Écho database is a provincial database which records acute care hospitalisation data for all Quebec residents; it also records gestational age for planned abortions, miscarriages and deliveries. Le fichier des événements démographiques du Québec (ISQ) provides demographic information on the mother, father and baby as well as birth weight and gestational age for live births and stillbirths.

To study the prevalence and risk of using NHPs during pregnancy on the newborn, a questionnaire would be sent to a random sample of women included in the Quebec Pregnancy Registry. The data obtained from the Quebec database may highlight frequently used NHPs in the first trimester of pregnancy. As per the challenges discussed above for the national and case-
control studies, adverse event associations (if any) will have to be interpreted with caution. This study is currently underway through Dr. Anick Berard at the Université de Montréal.

Motherisk Program prospective studies

The Motherisk Program has conducted a number of prospective cohort studies on pregnancy outcomes associated with NHP use: Echinacea\textsuperscript{71}, St. John’s wort\textsuperscript{51} and glucosamine sulfate\textsuperscript{72}. Through the Motherisk counselors, I will continue to develop and implement national prospective controlled observational studies of pregnancy outcomes after specific NHPs use in pregnancy. The challenge for MotherNature will be to increase enrollment to these studies through partners and stakeholders in Canada, the US, and worldwide. Since Motherisk counsels over 6,000 callers yearly on issues related to NHP use during pregnancy, it is ideally situated to design prospective cohort studies to determine safety and if safe, to design RCTs to determine efficacy.

Ex vivo common and cassia cinnamon placental transfer study

Since common and cassia cinnamon have been identified as having a low toxicity profile, these NHPs could be of therapeutic benefits to women with gestational diabetes electing not to undergo drug treatment. In order to determine if common and cassia cinnamon cross the placenta, they should undergo a placental transfer study.

In a placental transfer study, placenta would be obtained with informed consent after elective cesarean section delivery of non-complicated term pregnancies according to the inclusion and exclusion criteria listed below.

Inclusion: pregnant women, aged 18-45, over 37 weeks gestation, non-labouring, non-multiple pregnancy (twins, triplets, etc.).

Exclusion: non-pregnant women, aged <18 or > 45, below 37 weeks gestation, labouring, multiple pregnancy, women with major complications of pregnancy (including pre-eclampsia, hypertension, diabetes (gestational or mellitus), and premature labour), women with placental diseases, e.g. placenta previa, abrupto or insufficiency.
Using the human-perfused placental lobule technique, the placenta would be connected to both maternal and fetal circulation. Based on therapeutic doses administered in type 2 diabetics (Chapter 4), doses of common cinnamon would be added to the maternal circulation. The appearance of constituents of common cinnamon would be analyzed in the fetal circulation by chemiluminescence immunoassay. The experiment would be repeated at larger doses than the therapeutic dose, e.g. 10X, 100X and 1000X. The entire experiment would then be repeated for cassia cinnamon.
12 Conclusions

In total, 79 NHPs were systematically reviewed and 2 NHPs were meta-analyzed in this dissertation in order to determine the evidence of safety in pregnancy and lactation. In most cases, there were existing data on NHP safety during pregnancy, where only 7/79 NHPs did not have safety data in pregnancy. In lactation, 24/77 NHPs did not have safety data.

Despite the presence of data, the quality of the data was generally poor demonstrating a large knowledge gap on evidence of NHP safety in pregnancy and lactation. Using EBM principles, a new system of evaluating evidence was proposed for studies involving NHPs in pregnancy and lactation. The purpose of this model was to qualify NHP evidence in pregnancy and lactation in order to facilitate medical decision. This model requires further validation, both external and through future systematic reviews by this author.

A number of NHPs were identified as being of potential harm in pregnancy, including: deadly nightshade (*Atropa belladonna*), ephedra (*Ephedra* spp.), foxglove (*Digitalis lanata* and *D. purpurea*), calamus (*Acorus calamus*), juniper (*Juniperus communis*), pennyroyal (*Mentha pulegium*), parsley (*Petroselinum crispum* and *P. sativum*), barberry (*Berberis vulgaris*), goldenseal (*Hydrastis canadensis*) and Oregon gape (*Berberis aquifolium*). Of most concern, is blue cohosh (*Caulophyllum thalictroides*) which is commonly used to induce labour by midwives and has been linked with 3 serious cases of adverse effects, including perinatal stroke, acute myocardial infarction, profound congestive heart failure and shock, and severe multi-organ hypoxic injury. Based on its narrow therapeutic range, blue cohosh should be added to Schedule F of Canada’s Food and Drug Regulations.

A number of NHPs were identified as apparently safe in pregnancy, including: cranberry, echinacea, garlic, ginger, horsechestnut seed extract, Korean ginseng, milk thistle peppermint, raspberry, senna, St. John’s wort, fish oils, *LGG, L. reuteri, L. rhamnosus, B. breve, Propionibacterium freudenreichii*, and *B. lactis* and vitamins B6, D, E, K, B6 and folic acid. A number of NHPs were identified as apparently safe in lactation, including: borage oil, evening primrose oil, garlic, senna, *LGG, L. reuteri, L. rhamnosus, B. breve* and *Propionibacterium freudenreichii*, and vitamins A, D, E, K, B6 and folic acid.
Lastly, a network was created to forge longstanding relationships between medical and CAM practitioners, researchers and scientists; this network was called the MotherNature Network. Through work done in this dissertation and consultation with the MotherNature Network, I created a blueprint to conduct future studies on NHP safety in pregnancy and lactation.
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List of thesis publications

Textbooks


Scientific Journals


List of abbreviations

5-HTP: 5-hydroxytryptophan
ACE: Angiotensin converting enzymes
AIDS: Acquired immunodeficiency syndrome
BV: bacterial vaginosis
C-section: Caesarean section
CAM: complementary and alternative medicine
CFU: colony forming unit
EBMWG: Evidence-Based Medicine Working Group
GRAS: Generally regarded as safe
HA1c: Glycosylated hemoglobin
HIV: Human immunodeficiency virus
JAMA: Journal of the American Medical Association
LGG: *L. rhamnosus GG*
MSM: Methylsulfinylmethane
NHP: Natural health product
NHPD: Natural health Product Directorate
NHPs: Natural health products
NIH: National Institutes of Health (United States)
OCEBM: Oxford Center for Evidence-Based Medicine
PMS: Premenstrual syndrome
RCT: randomized controlled trial
Spp: Species
TGF-β: transforming growth factor β
UTI: Urinary tract infection
US: United States
USFDA: United States Food and Drug Administration
WHO: World Health Organization
Table 11.1: NHPs studied as part of this dissertation

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<tr>
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</tr>
<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>MSM</td>
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<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Quercetin</td>
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<td></td>
</tr>
<tr>
<td>5-HTP</td>
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<tr>
<td>Coenzyme Q10</td>
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<td></td>
</tr>
<tr>
<td>Fish oils</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Soy isoflavones</td>
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<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em> spp.</td>
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</tr>
<tr>
<td><em>Bifidobacterium</em> spp.</td>
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<td></td>
</tr>
<tr>
<td><em>Saccharomyces</em> spp.</td>
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<td></td>
</tr>
<tr>
<td>Common cinnamon</td>
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<tr>
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Table 11.2: NHPs with unknown evidence of safety in pregnancy and lactation

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<th>NHP</th>
<th>Harm or safety unknown in pregnancy</th>
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<tr>
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</tr>
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<td>√</td>
</tr>
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<td></td>
</tr>
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<td>Cranberry</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Damiana</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Dandelion</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Dong quai</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td>√</td>
<td></td>
</tr>
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<td>Guggul</td>
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<td>Hawthorn</td>
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<td></td>
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<tr>
<td>Horsechestnut</td>
<td>√</td>
<td></td>
</tr>
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<td>Milk thistle</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Peppermint</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Raspberry</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Siberian ginseng</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Squaw vine</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Valerian</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Wild yam</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>5-HTP</td>
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<tr>
<td>Coenzyme Q10</td>
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<td>n/a*</td>
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<td>Common cinnamon</td>
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</tr>
<tr>
<td>Cassia cinnmaon</td>
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* The safety of *Saccharomyces spp.* was not investigated in lactation as part of this dissertation.
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<th>1c</th>
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<td></td>
<td>blue cohosh</td>
<td>Blazing star</td>
<td>dandelion</td>
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</tr>
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<td>ephedra</td>
<td>echinacea</td>
<td></td>
<td>ashwaganda</td>
<td>MSM</td>
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<td></td>
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<td></td>
<td>fenugreek</td>
<td>damiana</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Garlic</td>
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</tr>
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<td>licorice</td>
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<td>fennel</td>
<td>feverfew</td>
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</tr>
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<td>Kava</td>
<td>parsley</td>
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<td>flax</td>
<td>guggul</td>
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<td></td>
<td>ginkgo</td>
<td>lemon balm</td>
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<td>vitamin A</td>
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<td></td>
<td>goldenseal</td>
<td>monkshood</td>
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<td></td>
</tr>
<tr>
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<td>vitamin D</td>
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<td>rye ergot</td>
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<td></td>
<td>Oregon grape</td>
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<tr>
<td></td>
<td>folic acid</td>
<td></td>
<td></td>
<td>red clover</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>fish oils</td>
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<td></td>
<td></td>
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</tr>
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<td></td>
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</tr>
<tr>
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Table 11.4: Highest level of evidence during lactation for NHPs studied

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<td>garlic</td>
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<td>green tea</td>
<td>fenugreek</td>
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<td>goldenseal</td>
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<td>ginkgo</td>
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<td>horsechestnut</td>
<td>guggul</td>
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</tr>
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<td>Yarrow</td>
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<td>valerian</td>
<td>green tea</td>
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<td>quercetin</td>
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<td>MSM</td>
<td>green tea</td>
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<td>coenzyme Q10</td>
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<td>cassia cinnamon</td>
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</table>
Table 11.5: Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)\(^5\)

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diagnosis/symptom prevalence study</th>
<th>Economic and decision analyses</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval(\ddagger))</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR† validated in a single population</td>
<td>Validating** cohort study with good†† reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none§</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts††</td>
<td>All or none case-series</td>
<td>Absolute better-value or worse-value analyses ††††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample$§§$ only</td>
<td>Exploratory** cohort study with good†† reference standards; CDR† after derivation, or validated only on split-sample$§§$ or databases</td>
<td>Retrospective cohort study, or poor follow-up</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; Research; Ecological studies</td>
<td>&quot;Outcomes&quot; Research</td>
<td>Ecological studies</td>
<td>Audit or outcomes research</td>
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</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
<td>Non-consecutive cohort study, or very limited population</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies$§$)</td>
<td>Case-series (and poor quality prognostic cohort studies$§§$)</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series or superseded reference standards</td>
<td>Analysis with no sensitivity analysis</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory or &quot;first principles&quot;</td>
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### Table 11.6: Levels of evidence for safety in pregnancy and lactation

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| 1a    | **Very Strong scientific evidence**  
Statistically significant evidence from one or more systematic reviews, meta-analyses or RCTs. |
| 1b    | **Strong Scientific evidence**  
Statistically significant evidence from one or more cohort studies OR control study. |
| 1c    | **Good Scientific evidence**  
Evidence from one or more case series. |
| 2     | **Fair Scientific evidence**  
Evidence based on case reports. |
| 3     | **In vitro scientific evidence**  
Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells. |
| 4     | **INDIRECT evidence**  
Evidence based on scientific theory OR expert opinion. |
| 5     | **Unknown**  
No available information. |
Appendix A

Chapter 4-6 from Herbal Medicines in Pregnancy and Lactation – An Evidence-Based Approach

Chapter 4

HERBAL MEDICINES

Herbal medicines are increasingly popular among the general public, particularly women of childbearing age. These medicines are not only viewed as having clinical benefit, but are generally believed to be safe. In some cases, a systematic review of the evidence based medicine literature shows that this is not the case.

In pregnancy, soon-to-be mothers are concerned about all medications that may affect their health, the health of their fetus and the pregnancy outcome. When it comes to the types of evidence for herbal medicines during pregnancy and lactation, not all evidence is created equally. The types of evidence for the safety of herbal medicines during pregnancy and lactation ranges from theoretical, to animal studies, to case reports, to cohort studies and finally, to randomized controlled trials.

This chapter is designed so that health care practitioners and mothers-to-be have the best available evidence-based safety information on the products they may choose, or not, to use during pregnancy and lactation.

In total, we selected 60 herbal medicines. In choosing these herbs, we set forth a number of selection criteria. These are outlined below.

- Herbs that are frequently used during pregnancy, e.g. black and blue cohosh, red raspberry, evening primrose oil
- Herbs that are used to treat pregnancy-related complaints, e.g. ginger
- Herbs that are known abortifacients, e.g. pennyroyal, parsley
- Herbs that have narrow therapeutic indices and are toxic, e.g. digitalis, deadly nightshade, ephedra
- Herbs that are used more often by women than men, e.g. red clover, don quai
• Herbs that are known to have hormonal effects, e.g. chaste tree

• The most-frequently used herbs, e.g. St. John’s wort (depression), garlic (hyperlipidemia), ginkgo (memory), Echinacea (immune system)

All 60 herbal medicine systematic reviews are presented as follows:

**Common name**

The name this herb is commonly referred to, e.g. garlic.

**Latin name**

The Latin name (genus, species) of this herb, e.g. *Allium sativum*. In some cases, more than one species of this herb has the same therapeutic effect, e.g. Panax sp.

**Synonyms**

Other names that this herb may be known as.

**Indications**

The main therapeutic indications for this herb. According to evidence-based medicines principles, the indications for this herb are evaluated based on grades of evidence (see Methodology section).

**Pregnancy**

The safety of this herb during pregnancy. According to evidence-based medicines principles, the safety of this herb during pregnancy is evaluated based on grades of evidence (see Methodology section).

**Lactation**

The safety of this herb during lactation. According to evidence-based medicines principles, the safety of this herb during lactation is evaluated based on grades of evidence (see Methodology section).
Contraindications

Conditions and diseases where this herb should not be taken.

Caution

Conditions or diseases where this herb should be used with caution.

Constituents

The main pharmacological constituents in this herb.

Toxicity

The toxicity of this herb (LD50, lethal dose, where available).

Pharmacology

General pharmacological properties of this herb.

Drug interactions

Drugs that may interact with this herb.

Parts Used

The part that has therapeutic benefits from this herb, e.g. root, leaf, stem, etc.
MONKSHOOD

_Aconitum napellus_

SYNONYMS AND COMMON NAMES

Wolfsbane, aconiti tuber, autumn monkshood, blue monkshood Root, chuan-wu, monkshood tuber, friar’s cap, mousebane, aconite

INDICATIONS

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic^2,3</td>
<td>E</td>
</tr>
<tr>
<td>Neuralgia^4</td>
<td>E</td>
</tr>
<tr>
<td>Ovarian cysts (as part of the Turska formula (Aconite, Bryonia, Phytolacca and Gelsemium))^5</td>
<td>F</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible central nervous system effects^6</td>
<td>4</td>
</tr>
</tbody>
</table>

An animal study was conducted on the effects of an alkaloid similar to aconitine, i.e. methyllycacoinitine (derived from _Delphinium brownii_)^6. The researchers reported that methyllycacoinitine was a potent antagonist of nAChR in the hippocampal neurons of rats^6.

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anovulatory effects^7</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that aconite had anovulatory effects _in vitro_^7.
**LACTATION**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible central nervous system effects⁶</td>
<td>4</td>
</tr>
</tbody>
</table>

An animal study was conducted on the effects of an alkaloid similar to aconitine, i.e. methyllycaconitine (derived from *Delphinium brownii*)⁶. The researchers reported that methyllycaconitine was a potent antagonist of nAChR in the hippocampal neurons of rats⁶.

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

Despite the apparent toxicity of this herb, there were no reports in the evidence-based medicine literature of monkshood being either safe or contraindicated during lactation.

**CONSTITUENTS**

Diterpene alkaloids⁸,⁹: aconitine (acetylbenzoylaconine), picraconitine (benzoylaconine), aconine, mesaconitine, napelline (isoaconitine, pseudoaconitine), hypaconitine, 3-acetylaconitine, lappaconitine, benzoaconine

Diterpenoid-ester alkaloids⁸,⁹

**TOXICOLOGY**

Monkshood is one of the most poisonous plants known. There are a number of case reports of accidental poisonings¹⁰-¹⁶.

Lethal dose⁸,⁹,¹⁷: 1 g (powdered herb), 5 ml (tincture), 3-6 mg of aconitine

**PHARMACOLOGY**

Monkshood alkaloids have anti-nociceptive effects and can be useful analgesics².

Monkshood alkaloids have muscarinic effects where they stimulate the parasympathetic nervous system, causing bradycardia and hypotension⁸.
The constituent lappaconitine is an antagonist of both sodium and calcium channels, thereby causing anti-arrhythmia and bradycardia effects\textsuperscript{2,8}.

**PARTS USED\textsuperscript{8}**

Whole herb

**REFERENCES**


ALFALFA

Medicago sativa

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Feuille de luzerne, lucerne, medicago, phytoestrogen, purple medick

INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal symptoms (with sage)</td>
<td>B2</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
<td>D</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>E</td>
</tr>
<tr>
<td>Diabetes</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Estrogenic activity</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

A study on the effects of dietary genistein exposure during development found that dietary genistein produced effects in multiple estrogen-sensitive tissues in both male and female rats. Another study reported estrogenic activity of genistein and diadzein in human cells in vitro and in rats. The phytoestrogen coumestrol, contained in alfalfa, was reported to be 35 times more potent than the phytoestrogens genistein, biochanin A, formononetin and daidzein. A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa has estrogenic activity.
<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated compounds have uterine stimulating activity(^14)</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa was a uterine stimulant and that its constituent stachydrine was a uterine stimulant\(^14\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue(^15)</td>
</tr>
</tbody>
</table>

A herbal medicine compendium reported that alfalfa is an emmenagogue\(^15\). There are no reports in the evidence-based medicine literature of alfalfa being an emmenagogue.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigonadotrophic activity(^14)</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa had antigonadotrophic activity in rats where the acid extract interfered with seminal vesicle growth and potentiated the action of estrogens\(^14\).

**Consumed as Food**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^15)-(^18)</td>
</tr>
</tbody>
</table>

In a study on the effects of alfalfa feeding on pregnancy and lactation in beef heifers, no adverse effects were reported when alfalfa was consumed in food amounts\(^16\). A herbal medicine compendium reported that when consumed as food, alfalfa is believed to be of minimal risk\(^15\).
LACTATION

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogenic activity\textsuperscript{10-12}</td>
</tr>
</tbody>
</table>

A study on the effects of dietary genistein exposure during development found that dietary genistein produced effects in multiple estrogen-sensitive tissues in both male and female rats\textsuperscript{10}. Another study reported estrogenic activity of genistein and diadzein in human cells \textit{in vitro} and in rats\textsuperscript{11}. The phytoestrogen coumestrol, contained in alfalfa, was reported to be 35 times more potent than the phytoestrogens genistein, biochanin A, formononetin and daidzein\textsuperscript{12}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactogenic\textsuperscript{14}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that alfalfa seeds may be lactogenic\textsuperscript{14}.

Consumed as Food

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{15-17}</td>
</tr>
</tbody>
</table>

In a study on the effects of alfalfa feeding on pregnancy and lactation in beef heifers, no adverse effects were reported with alfalfa consumed in food amounts\textsuperscript{16}. A herbal medicine compendium reported that when consumed as food, alfalfa is believed to be of minimal risk\textsuperscript{15}.

CONTRAINDICATIONS

Systemic Lupus Erythmatosus (SLE)\textsuperscript{19,20}

CAUTION

Hormone sensitive conditions such as breast, uterine, or ovarian cancer, endometriosis and fibroids\textsuperscript{12,21}
Diabetes$^{15}$

CONSTITUENTS

Saponins$^{15, 22}$

Flavonoids$^{23}$,

Phytoestrogens$^{1, 12, 24}$: coumestrol, genistein, biochanin A, and daidzein

Vitamins A, C, E, and K$^{15}$

Manganese$^{15, 25}$

Stachydrine$^{14}$

TOXICITY

In a six-week study, no signs of toxicity were reported in six humans consuming 160 grams a day of alfalfa for three weeks followed by 80 grams of alfalfa a day for three weeks$^5$.

PHARMACOLOGY

The phytoestrogens coumestrol, genistein, biochanin A and daidzein have been shown to have estrogenic properties$^{10-12, 24}$.

The saponin constituents in alfalfa leaves were shown to decrease total cholesterol levels without affecting HDL levels$^{15}$.

Alfalfa constituents may decrease cholesterol absorption and increase fecal excretion of neutral steroids and bile acids$^{15, 26}$.

Alfalfa contains manganese which might be responsible for its hypoglycemic effects$^{15}$.

Alfalfa contains medicagol, which appears to have antifungal properties$^1$.

DRUG INTERACTIONS$^1$

Anticoagulants$^{15}$
Photosensitizing drugs
Oral contraceptives
Hormone therapy
Warfarin (coumadin)

PARTS USED
Above ground parts

REFERENCES


ALOE

*Aloe spp.*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

*Aloe vera (Aloe barbadensis), Aloe ferox, Aloe africana, Aloe arborescens natalenis, Aloe capensis*, aloe leaf gel, *Aloe perfoliata, Aloe perryi, Aloe spicata*, salvia, cape aloes, Barbados aloe, Curacao aloe, hepatic aloes, aloe dried juice from leaf, aloe juice, burn plant, elephant's gall, hsiang-dan, lily of the desert, lu-hui, miracle plant, plant of immortality

INDICATIONS

Oral

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic constipation&lt;sup&gt;2-6&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Solid tumours (with melatonin)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Elevated cholesterol and triglycerides, hyperglycemia and low HDL cholesterol (with husk of isabgol)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Chronic venous leg ulcers&lt;sup&gt;9&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Fibromyalgia, chronic fatigue syndrome&lt;sup&gt;10&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Diabetes Type II&lt;sup&gt;11-13&lt;/sup&gt;</td>
<td>E</td>
</tr>
<tr>
<td>Bronchial asthma (aloe vera gel)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>E</td>
</tr>
</tbody>
</table>
Topical

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis vulgaris\textsuperscript{15}</td>
<td>B1</td>
</tr>
<tr>
<td>Herpes simplex type II\textsuperscript{16, 17}</td>
<td>B1</td>
</tr>
<tr>
<td>Seborrheic dermatitis\textsuperscript{18}</td>
<td>B1</td>
</tr>
<tr>
<td>Radiation induced dermatitis\textsuperscript{19}</td>
<td>B2</td>
</tr>
<tr>
<td>Occupational dry skin, irritant contact dermatitis\textsuperscript{20}</td>
<td>B2</td>
</tr>
<tr>
<td>Burn wounds\textsuperscript{21}</td>
<td>C</td>
</tr>
<tr>
<td>Alveolar osteitis\textsuperscript{22}</td>
<td>C</td>
</tr>
<tr>
<td>Chronic venous leg ulcers\textsuperscript{9}</td>
<td>C</td>
</tr>
<tr>
<td>Anti-arthritic, anti-inflammatory \textit{(Aloe africana)}\textsuperscript{23}</td>
<td>E</td>
</tr>
<tr>
<td>Anti-inflammatory \textit{(Aloe vera)}\textsuperscript{24}</td>
<td>E</td>
</tr>
<tr>
<td>Wounds \textit{(Aloe vera)}\textsuperscript{24, 25}</td>
<td>E</td>
</tr>
</tbody>
</table>

**PREGNANCY**

Oral

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially nephrotoxic\textsuperscript{26}</td>
<td>2</td>
</tr>
<tr>
<td>Potential hepatic dysfunction\textsuperscript{26}</td>
<td>2</td>
</tr>
</tbody>
</table>

A case of acute oliguric renal failure and liver dysfunction was reported in the literature following traditional therapeutic use of cape aloes\textsuperscript{26}. 
A review article on the potential value of plants as sources of anti-fertility agents reported that aloe species are potential abortifacients and emmenagogues.

Aloe-emandin, a 1,8-dihydroxyanthraquinone found in aloe, is potentially carcinogenic, mutagenic and genotoxic in mice.

Topical

A herbal medicine compendium reported that the external use of aloe vera gel is not a concern during pregnancy. The external use of aloe was not reported in the evidence-based literature as contraindicated or safe during pregnancy or lactation.
LACTATION

Oral

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially genotoxic(^3,28,29)</td>
<td>3</td>
</tr>
<tr>
<td>Potentially mutagenic(^3,28,29)</td>
<td>3</td>
</tr>
<tr>
<td>Potentially carcinogenic(^3,28,29)</td>
<td>3</td>
</tr>
</tbody>
</table>

Although it is unclear if aloe components cross into breast milk, these components are potentially genotoxic/mutagenic and carcinogenic to the nursing infant\(^3,28,29\).

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid during lactation(^3,31)</td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal safety and drug-interaction compendium and a herbal medicine compendium reported that aloe species should be avoided during lactation\(^3,31\).

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential laxative(^3,28)</td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal safety and drug-interaction compendium and a herbal medicine compendium reported that aloe species may cause diarrhea in the infant due to aloe’s laxative effect\(^3,28\).

Topical

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use with caution</td>
<td>4</td>
</tr>
</tbody>
</table>

Infants nursing from a breast where aloe has been topically applied may be susceptible to the same risks as if aloe components where ingested.
CONTRAINDICATIONS$^{2,3,26,30,32}$

Menstruation (especially menorrhagia and metrorrhagia)

Actively inflamed hemorrhoids

Intestinal obstruction

Acutely inflamed intestinal diseases (e.g. Crohn's disease, ulcerative colitis, appendicitis)

Abdominal pain of unknown origin

Kidney dysfunction

Children under 12 years of age

CAUTION

Use for more than 8-10 days

Post-surgical wounds$^{33}$

CONSTITUENTS

Anthroquinone glycosides$^{3,30}$: aloin A, aloin B, aloinoside A, aloinoside B, 7-hydroxyaloins, emodin

Anthraquinone$^{34}$: aloe-ewoodin (1,8-Dihydroxyanthraquinone)

Aloresin A$^{30}$

TOXICOLOGY

Aloe-ewoodin is potentially carcinogenic and genotoxic$^{29,35}$.

Acemannan exhibited significant cytotoxicity to human gingival fibroblasts; however, in animals, oral adminstration of acemann was found to be safe$^{36-38}$. 
PHARMACOLOGY

The anthraquinones (dried latex) in aloe exert a laxative and purgative effect whereas aloe gel does not\(^3\).

Aloe and aloe gum may have a hypoglycemic effect\(^{11-13}\).

With husk of Isabgol, aloe significantly reduced total cholesterol, triglycerides, fasting and post prandial blood sugar levels in diabetic patients and total lipids, and increased HDL cholesterol\(^8\).

Aloe vera gel was shown to delay wound healing in women following cesarean delivery or laparotomy\(^3\).

Topical application *Aloe africana* was found to have an anti-arthritis and anti-inflammatory effects\(^2\).

Aloe vera gel was found to enhance phagocytosis in human bronchial asthma\(^4\).

Aloe vera gel was found to reduce pruritis by inhibiting thromboxane formation *in vivo*, inactivating bradykinin *in vitro* and inhibiting histamine\(^3\).

Aloe vera gel may have antibacterial and antifungal effects\(^3\).

The addition of aloe vera gel to a mild soap had a protective effect on the skin of patients undergoing radiation therapy\(^1\).

DRUG INTERACTIONS

Antiglycemic drugs\(^{11-13}\)

Cardiac glycosides\(^3\)

Diuretics\(^2\)

Oral drugs\(^3\)
PARTS USED\textsuperscript{3,30}

Dried latex and gel from leaves

REFERENCES


ASHWAGANDHA

*Withania somnifera*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Ajagandha, amangura, amukkirag, asan, asgand, asgandh, asgandha, ashagandha, ashvagandha, ashwaganda, asoda, asundha, asvagandha, avarada, ayurvedic Ginseng, clustered wintercherry, ghoda asoda, Indian ginseng, kanaje hindi, kuthmithi, samm al ferakh, turangi-ghanda, winter cherry, withania.

**INDICATIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis (with boswellia, turmeric and zinc)</td>
<td>B2</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>C</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>C</td>
</tr>
<tr>
<td>Stress</td>
<td>E</td>
</tr>
<tr>
<td>Cancer</td>
<td>E</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces fertility</td>
<td>3</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that ashwaghanda caused a reduction in fertility in rats.
A review article on the potential value of plants as sources of anti-fertility agents reported that ashwaghandha was a potential abortifacient and that its constituent, nicotine, was a uterine stimulant.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortifacient&lt;sup&gt;7, 8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uterine stimulant constituent&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of ashwaghandha being either safe or contraindicated during lactation.

**CONSTITUENTS**

Alkaloids<sup>9, 10</sup>: isopelletierine, anaferine

Steroidal lactones<sup>9-11</sup>: withanolides, aithaferins

Saponins<sup>9, 10</sup>

**TOXICITY**

LD<sub>50</sub> (intraperitoneal)<sup>12</sup>: 432 to 465 mg/kg

Doses of 1000mg/kg produced fatalities in mice<sup>13</sup>.

Doses of 500-750mg/kg given to total cumulative doses of 7.5-10g were apparently safe<sup>13</sup>. 
PHARMACOLOGY

Ashwagandha was reported to have analgesic, antipyretic, anxiolytic, immunomodulatory, sedative, hypotensive, anti-inflammatory, and antioxidant effects\(^1,9,10,14-16\).

During stress, ashwagandha suppresses the increases of plasma corticosterone, blood urea nitrogen, blood lactic acid and the increase of dopamine receptors in the corpus striatum of the brain\(^9,14\).

Ashwaghanda may have anxiolytic effects by acting as a gamma-aminobutyric acid (GABA) mimetic agent and anticonvulsant activity by binding to GABA receptors\(^14\).

Ashwaghanda stimulates respiratory function, smooth muscle relaxation, and thyroid hormone synthesis and secretion\(^14\).

The ashwagandha constituents withanolides cause a mobilization of macrophages, phagocytosis, and lysosomal enzymes\(^9\).

Ashwaghanda reduces cyclophosphamide-induced immunosuppression and leukopenia and increases bone marrow cell and white blood cell count in radiation-treated animals\(^15,17\).

Ashwaghanda has diuretic effects\(^3\).

DRUG INTERACTIONS

Benzodiazepines\(^14\)

CNS Depressants\(^14\)

Immunosuppressant drugs\(^15,17\)

Thyroid hormone\(^14\)

PARTS USED

Root and berry
REFERENCES


11. Abou-Douh AM. New withanolides and other constituents from the fruit of Withania somnifera. Arch Pharm (Weinheim) 2002; 335:267-76.


# ASTRAGALUS

*Astragalus membranaceus*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**

Astragali, beg kei, bei qi, buck qi, huang qi, huang qi, hwanggi, membranous milk vetch, milk vetch, Mongolian milk, ogi

## INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis (within a Chinese herbal preparation)</td>
<td>B2</td>
</tr>
<tr>
<td>HIV (within a Chinese herbal preparation)</td>
<td>B2</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>B2</td>
</tr>
<tr>
<td>Minimal brain dysfunction</td>
<td>B2</td>
</tr>
<tr>
<td>Immune stimulation</td>
<td>C</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>C</td>
</tr>
<tr>
<td>Chemotherapy side effects</td>
<td>C</td>
</tr>
<tr>
<td>Post-acute myocardial infarction</td>
<td>C</td>
</tr>
<tr>
<td>Acute viral myocarditis (with drugs and other supplements)</td>
<td>C</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>C</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>C</td>
</tr>
<tr>
<td>Liver protection</td>
<td>E</td>
</tr>
<tr>
<td>Cancer</td>
<td>E</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>E</td>
</tr>
</tbody>
</table>
PREGNANCY

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There is no report in the evidence-based literature of astragalus being either safe or contraindicated during pregnancy.

Other Astragalus species

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsafe during pregnancy</td>
</tr>
<tr>
<td>Estrogenic</td>
</tr>
</tbody>
</table>

Other *Astragalus* species, such as *Astragalus lentiginosus* or *Astragalus mollissimus* (locoweed), have been reported to have harmful effects during animal pregnancies\(^1\)\(^,\)\(^2\). Ingestion of locoweed (*Astragalus* species) by pregnant livestock may result in fetal malformations, delayed placentation, reduced placental and uterine vascular development, hydrops amnii, hydrops allantois, abnormal cotyledonary development, interruption of fetal fluid balance, and abortion\(^1\)\(^,\)\(^2\). During pregnancy, the toxic agent in locoweed (swainsonine) is believed to pass through the placental barrier to the fetus\(^1\)\(^,\)\(^2\). A review article on the potential value of plants as sources of anti-fertility agents reported that *Astragalus hypogaea, lentiginosus, miser* and *sinicus* have estrogenic activity\(^1\). *Astragalus membranaceus* is not reported in the evidence-based literature as containing the toxic agent swainsonine.

LACTATION

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There is no report in the evidence-based literature of astragalus being either safe or contraindicated during lactation.
Other Astragalus species

<table>
<thead>
<tr>
<th>Grade</th>
<th>Unsafe during lactation (^{18})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

During lactation, the toxic agent in locoweed (swainsonine) is believed to pass through the milk to the neonate \(^{18}\). *Astragalus membranaceus* is not reported in the evidence-based literature as containing the toxic agent swainsonine.

**CONSTITUENTS** \(^{20, 21}\)

Saponins: astragaloside

Flavonoids

Polysaccharides

Coumarins

Trace minerals

Amino acids

**TOXICITY**

LD\(_{50}\) in mice (intraperitoneal): 39.8g/kg \(^{22}\).

Doses greater than 28 grams per day may cause immunosuppression \(^{21}\).

Aqueous extracts of 1.25mg/ml modestly increased the incidence (16%) of aberrant cells *in vitro* \(^{23}\).

**PHARMACOLOGY**

Astragalus is an antioxidant where it inhibits free radical production, increases superoxide dismutase, and decreases lipid peroxidation \(^{21}\).
Astragalus is an immune stimulant by increasing the effects of interferon, by increasing antibody levels of IgA and IgG in nasal secretions, by improving the response of mononuclear cells and by stimulating lymphocyte production\textsuperscript{7,21}.

Astragalus may restore or improve immune function in cases of immune deficiency\textsuperscript{7,24}.

Lower doses appear to stimulate the immune system, while doses in excess of 28 grams per day may suppress immunity\textsuperscript{21}.

Astragalus may increase proliferation and differentiation of bone marrow stem cells and progenitor cells when administered intravenously\textsuperscript{21}.

Astragalus decreases liver enzymes serum glutamate pyruvate transaminase (SGPT) and alanine aminotransferase (ALT)\textsuperscript{2,15,21}.

Astragalus causes vasodilation and increases cardiac output\textsuperscript{21}.

Astragalus has antibacterial activity\textsuperscript{21}.

**DRUG INTERACTIONS**

Cyclophosphamide\textsuperscript{21,24}

Immunosuppressants\textsuperscript{21}

**PARTS USED**

Root\textsuperscript{1}

**REFERENCES**


BARBERRY

*Berberis vulgaris*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

European barberry, pepperidge, sow berry, jaundice berry, berberry, berbis, common barberry, epine-vinette, espino cambrón, piperidge, piprage, sauerdorn, vinettier, agracejo, *Berberidis cortex*, *Berberidis fructus*, *Berberidis radicis cortex*, *Berberidis radix*, berberitze

INDICATIONS

**Berberine**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine-resistant malaria (with pyrimethamine)</td>
<td>B1</td>
</tr>
<tr>
<td>Infectious diarrhea</td>
<td>B1</td>
</tr>
<tr>
<td>Trachoma (<em>Chlamydia trachomatis</em> eye infection)</td>
<td>B2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>C</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>E</td>
</tr>
<tr>
<td><em>Anti-Helicobacter pylori</em></td>
<td>E</td>
</tr>
<tr>
<td>Cancer prevention</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause newborn jaundice (ker nicterus)</td>
<td>3</td>
</tr>
</tbody>
</table>

In rats, berberine displaces bilirubin bound to albumin. Berberine (10-20 ug/g) was administered intraperitoneally to adult rats on a daily basis for 1 week. After one week, a
significant decrease in mean bilirubin serum protein binding was observed, due to an in vivo displacement effect by berberine\textsuperscript{14}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{14}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant\textsuperscript{15,16}</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that barberry was a uterine stimulant\textsuperscript{16}. The alkaloids palmatine, berberine, jatrorrhizine and columbamine, contained in barberry, are believed to act as uterine stimulants\textsuperscript{15,17}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause or aggravate newborn jaundice (kernicterus)\textsuperscript{14}</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

In rats, berberine displaces bilirubin bound to albumin\textsuperscript{14}. Berberine (10-20 ug/g) was administered intraperitonealy to adult rats on a daily basis for 1 week\textsuperscript{14}. After one week, a significant decrease in mean bilirubin serum protein binding was observed, due to an in vivo displacement effect by berberine\textsuperscript{14}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{14}.

**CONTRAINDICATION**

Newborn jaundice (kernicterus)\textsuperscript{14}

**TOXIC CONSTITUENTS**

Isoquinoline alkaloids\textsuperscript{17}: oxyacanthine, berbamine, berberine, palmatine, jatrorrhizine, columbamine

Tannins\textsuperscript{17}

**TOXICOLOGY**

LD\textsubscript{50} of berberine in humans\textsuperscript{15}: 27.5 mg/kg
PHARMACOLOGY

Berberine was found to displace bilirubin bound to albumin in vitro\textsuperscript{14}. Berberine was found to be about ten times superior to phenylbutazone, a known potent displacer of bilirubin, and about one hundred times superior to papaverine, a berberine-type alkaloid\textsuperscript{14}.

The constituents berberine and oxyacanthine have been shown to have antibacterial activity\textsuperscript{8,9,18,19}.

Berberine has been shown to have amebicidal, anti-parasitic (trypanocidal) and anti-fungal activity\textsuperscript{18,20-22}.

Berberine and beta-hydrastine were shown to have anti-\textit{Helicobacter pylori} activity in vitro\textsuperscript{10}.

In low doses, berberine may act as a cardiac and respiratory stimulant, while in high doses it may act as a cardiac and respiratory depressant\textsuperscript{15,18,23}.

Berberine was shown to have anti-platelet activity\textsuperscript{24}.

Berberine, oxyacanthine and barbamine were shown to have anti-inflammatory effects\textsuperscript{25-28}.

Berberine was found to have an antidiarrheal effects\textsuperscript{29}.

Berberine was found to inhibit parathyroid hormone (PTH)-stimulated bone resorption, inhibit osteoclastic bone resorption and prevent a decrease in bone mineral density of the lumbar vertebra\textsuperscript{30}.

DRUG INTERACTIONS

Anticoagulant drugs\textsuperscript{24}

Highly protein bound drugs\textsuperscript{14}

PARTS USED\textsuperscript{17}

Root
References


BLACK COHOSH

*Cimicifuga racemosa*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Baneberry, black snakeroot, bugbane, bugwort, cimicifuga, macrotys, phytoestrogen, rattle root, rattle snakeroot, rattle top, rattlesnake root, rattleweed, snakeroor, squaw root, squawroot

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal symptoms(^2-4)</td>
<td>B1</td>
</tr>
<tr>
<td>Arthritis pain (with white willow bark, sarsaparilla, poplar bark and guaiacum resin)(^5)</td>
<td>B2</td>
</tr>
<tr>
<td>Induction of labour(^6)</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induces labour(^6)</td>
<td>4</td>
</tr>
</tbody>
</table>

A survey of midwives in the United States found that 45% of midwives use black cohosh to induce labour\(^6\). Black cohosh is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to black cohosh, mother’s cordial contains: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), blue cohosh (*Caulophyllum thalictroides*) and false unicorn (*Chamaelirium luteum*).
It is unclear if black cohosh has an estrogenic and/or an anti-estrogenic effect⁷. Nonetheless, a review article recommended that black cohosh be avoided during pregnancy due to its potential hormonal effect⁷.

A herbal contraindication and drug interaction compendium reported that black cohosh was an emmenagogue and contraindicated during pregnancy, particularly in the first trimester⁸.

A review article on the potential value of plants as sources of anti-fertility agents reported that black cohosh had anovulatory effects *in vitro*⁹.

**LACTATION**

It is unclear if black cohosh has an estrogenic and/or an anti-estrogenic effect⁷. Nonetheless, a review article recommended that black cohosh be avoided during lactation due to its potential hormonal effect⁷.
CONSTITUENTS

Triterpene glycosides: acetin, cimicifugoside, 27-deoxyacetin
Organic acids: isoferulic acid, cimicifugic acids (A, B, E and F), fukinolic acid, caffeic acid, salicylic acid
Cimicifugin
Tannins
Phytosterin

PHARMACOLOGY

In some studies, black cohosh constituents bind to estrogen receptors in vitro or have an estrogenic effect. In other studies, black cohosh estrogenic or estrogen receptor-binding effects were not found.

Black cohosh antagonizes the proliferation of cells induced by estradiol in vitro, thereby having anti-estrogenic activity.

Black cohosh decreases luteinizing hormone (LH) levels, but has no effect on follicular stimulating hormone (FSH) levels.

Black cohosh inhibits the growth of human breast cancer cells in vitro.

Black cohosh has anti-inflammatory effects where the constituents caffeic acid, fukinolic acid and cimicifugic acids (A, B, E, F) were found to inhibit neutrophil elastase activity in vitro.

Black cohosh possesses a central activity instead of a hormonal effect.

DRUG INTERACTIONS

Docetaxel
Doxorubicin
PARTS USED

Roots, rhizome

REFERENCES


BLAZING STAR

*Aletris farinosa*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES\(^1,2\)

Ague grass, ague Root, aloerot, colic root, crow corn, devil's-bit, stargrass, starwort, true-unicorn root, unicorn root, whitetube stargrass

INDICATIONS

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual complaints(^3)</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant(^4)</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that blazing star was a uterine stimulant\(^4\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine relaxant(^1,5)</td>
</tr>
<tr>
<td>Estrogenic(^6)</td>
</tr>
</tbody>
</table>

A herbal safety and drug interaction compendium reported that blazing star was a uterine relaxant\(^1,5\). A botanical safety compendium reported that blazing star has estrogenic and oxytocic activity\(^6\). There are no reports in the evidence-based medical literature of blazing star having estrogenic or oxytocic activity nor are there reports that blazing star is contraindicated or safe during pregnancy.
LACTATION

<table>
<thead>
<tr>
<th>Oxytoxin antagonism</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

A botanical safety compendium reported that blazing star has estrogenic and oxytoxic activity. There are no reports in the evidence-based medical literature of blazing star having estrogenic or oxytoxic activity nor are there reports that blazing star is contraindicated or safe during lactation.

CONTRAINDICATION

Infectious or inflammatory gastrointestinal conditions

CAUTION

Hormone sensitive cancers (breast, uterine and ovarian)

Endometriosis

Uterine fibroids

CONSTITUENTS

Diosgenin, volatile oils and resin

PHARMACOLOGY

Aletris was found to be estrogenic.

Diosgenin is one of the starting hormones use in the manufacturing of steroid hormones. Aletris may increase stomach acid secretion.

Aletris is an irritant to the gastrointestinal tract.

DRUG INTERACTIONS

Oxytocin drugs
Acid-inhibiting drugs

PARTS USED

Root

References


BLUE COHOSH

Caulophyllum thalictroides

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Blue ginseng, caulophyllum, papoose root, squaw root, yellow ginseng

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of labour</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
</tr>
</tbody>
</table>

There is one report of a newborn infant whose mother ingested blue cohosh to promote uterine contractions. The newborn presented at birth with acute myocardial infarction associated with profound congestive heart failure and shock. The infant remained critically ill for several weeks, although he eventually recovered. The authors reported that all other causes of myocardial infarction were carefully excluded. The authors believed that these observed effects were due to the vasoactive glycosides and an alkaloid of blue cohosh known to produce toxic effects on the myocardium.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe multi-organ hypoxic injury</td>
<td>2</td>
</tr>
</tbody>
</table>

There is one report of severe multi-organ hypoxic injury in a child delivered "naturally" with the aid of both blue and black cohosh (Caulophyllum thalictroides) who was not breathing at the time of birth. The child survived with permanent central nervous system damage. Blue cohosh possesses a vasoconstrictive glycoside which may have been responsible for the adverse effects.
A 21-y-old female developed signs of nicotinic toxicity, i.e., tachycardia, diaphoresis, abdominal pain, vomiting and muscle weakness and fasciculations, after using blue cohosh in an attempt to induce an abortion. The saponins in blue cohosh are believed to be responsible for the uterine stimulant effect. A review article on the potential value of plants as sources of anti-fertility agents also reported that blue cohosh was a potential abortifacient, emmenagogue and uterine stimulant.

<table>
<thead>
<tr>
<th>Grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortifacient</td>
<td>2</td>
</tr>
<tr>
<td>Uterine stimulant</td>
<td>2</td>
</tr>
<tr>
<td>Emmenagogue</td>
<td>4</td>
</tr>
</tbody>
</table>

The alkaloid methylcystisine, a constituent of blue cohosh, was shown to be teratogenic in rats. The alkaloid taspine, a constituent of blue cohosh, was shown to be highly embryotoxic in rats.

<table>
<thead>
<tr>
<th>Grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratogenic</td>
<td>4</td>
</tr>
<tr>
<td>Embryotoxic</td>
<td>4</td>
</tr>
</tbody>
</table>

A compendium for medicinal plants reported that blue cohosh may have oxytotic effects. Blue cohosh was not reported in the evidence-based medicine literature as having an oxytotic effect.

<table>
<thead>
<tr>
<th>Grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytotic</td>
<td>4</td>
</tr>
</tbody>
</table>

A survey of midwives in the United States found that 64% of midwives use blue cohosh to induce labour. Blue cohosh is part of a combination of herbal medicines that have been traditionally...
used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to blue cohosh, mother’s cordial contains: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), black cohosh (*Cimicifuga racemosa*) and false unicorn (*Chamaelirium luteum*).

**Homeopathic Blue Cohosh (Caulophyllum)**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not induce labour(^{11,12})</td>
</tr>
</tbody>
</table>

A systematic review concluded that there is insufficient evidence to recommend the use of homeopathic blue cohosh as a method of inducing of labour\(^{11,12}\). Although caulophyllum is a commonly used homeopathic therapy to induce labour, the treatment strategy used in this review may not reflect routine practice of homeopathy. A homeopathic preparation of *Caulophyllum thalictroides*, called Caulophyllum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance.

**LACTATION**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible cardiotoxic effects(^3)</td>
</tr>
</tbody>
</table>

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals\(^3\). Blue cohosh is not reported in the evidence-based medicine literature as being either contraindicated or safe in lactation.

**CONSTITUENTS**

Triterpene saponins\(^{10,13}\): caulophyllogenin, hederagenin, caulosaponin

Alkaloids\(^9\): thalictroidine, taspine, magnoflorine, anagyrine, baptifoline, 5,6-dehydro-alpha-isolupanine, alpha-isolupanine, lupanine, N-methylcytisine, sparteine
TOXICOLOGY

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals\(^3\).

Blue cohosh was reported to constrict coronary arteries and to decrease the flow of oxygen to the heart\(^{14}\).

The alkaloid methylcytisine was shown to cause symptoms of nicotinic toxicity\(^7\).

Methylcytisine was shown to be teratogenic in rats\(^9\).

Taspine was shown to be embryotoxic in rats\(^9\).

PHARMACOLOGY

Blue cohosh extract was shown to enhance estradiol binding to estrogen receptors and to increase estradiol-induced transcription activity in estrogen-responsive cells\(^1\).

Blue cohosh was shown to decrease luteinizing hormone (LH) levels and to increase serum ceruloplasmin oxidase activity, which are measures of estrogenic activity in the liver\(^1\).

DRUG INTERACTIONS

Anti-diabetic Drugs\(^1\)

Cardiovascular Drugs\(^3,10\)

Nicotine\(^7\)

PARTS USED\(^1\)

Rhizome and root

References


BORAGE

*Borago officinalis*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES\(^1\)

Borage oil, bugloss, burage, burrage, huile de bourrache, starflower

INDICATIONS

Oral

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis(^2)</td>
<td>B1</td>
</tr>
<tr>
<td>*Atopic dermatitis (^3-6)</td>
<td>B1</td>
</tr>
<tr>
<td>Adult periodontitis(^7)</td>
<td>B1</td>
</tr>
<tr>
<td>Attenuates stress(^8)</td>
<td>B2</td>
</tr>
<tr>
<td>Hyperlipidemia(^9)</td>
<td>C</td>
</tr>
<tr>
<td>Atherosclerosis prevention(^9)</td>
<td>C</td>
</tr>
<tr>
<td>Skin irritation(^10)</td>
<td>C</td>
</tr>
<tr>
<td>Gastric cancer prevention(^11)</td>
<td>D</td>
</tr>
<tr>
<td>Hypertension(^12)</td>
<td>E</td>
</tr>
</tbody>
</table>

* One randomized controlled trial reported that several clinical symptoms of atopic dermatitis improved compared with placebo, but the overall response to borage oil did not reach statistical significance\(^6\). This study, however, found statistically significant benefits of borage oil on atopic dermatitis in a subgroup of the research subjects\(^6\).
### Eneral

<table>
<thead>
<tr>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome (ARDS) (with eicosapentaenoic acid (EPA; fish oil) and antioxidants)(^\text{13})</td>
</tr>
</tbody>
</table>

### Topical

<table>
<thead>
<tr>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Infantile seborrhic dermatitis(^\text{14})</td>
</tr>
</tbody>
</table>

### PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Teratogenic and induces labour(^\text{15})</td>
</tr>
</tbody>
</table>

A review of randomized double blind studies was conducted on the benefit of borage oil in the treatment of rheumatoid arthritis\(^\text{15}\). Evidence from published research indicated that the gamma linolenic acid (GLA) component of borage oil increases prostaglandin E levels\(^\text{15}\). It was recommended that borage oil be contraindicated in pregnancy given the teratogenic and labor inducing effects of prostaglandin E agonists\(^\text{15}\).

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Minimal risk(^\text{16})</td>
</tr>
</tbody>
</table>

A study compared the effects of diets containing gamma-linolenic acid (GLA) from borage oil and other sources on reproduction, pup development and pup brain fatty acid composition in mice\(^\text{16}\). An increase in dietary GLA resulted in an increase in brain long chain n-6 fatty acids (20:4n-6 and 22:4n-6)\(^\text{16}\). The authors did not report any adverse effects associated with the ingestion of borage oil\(^\text{16}\).
Borage oil has been reported to contain small amounts of pyrrolizidine alkaloids\textsuperscript{20}. Pyrrolizidine alkaloids are hepatotoxic, pneumotoxic, genotoxic, neurotoxic and cytotoxic, and may cause hepatic veno-occlusive disease\textsuperscript{18,19}. A compendium on complementary and alternative medicine reported that therapeutic doses of borage seed oil can provide amounts of pyrrolizidine alkaloids that can reach toxic levels\textsuperscript{21}. Borage seed oil containing pyrrolizidine alkaloids, dosed at 1-2 grams per day, may provide approximately 10 ug of pyrrolizidine alkaloids, which exceeds the German Commission E recommendation by 10 times\textsuperscript{21,22}.

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetotoxic\textsuperscript{17}</td>
<td>4</td>
</tr>
<tr>
<td>Mutagen\textsuperscript{17}</td>
<td>4</td>
</tr>
<tr>
<td>Hepatotoxic\textsuperscript{18,19}</td>
<td>4</td>
</tr>
<tr>
<td>Pneumotoxic\textsuperscript{18,19}</td>
<td>4</td>
</tr>
<tr>
<td>Genotoxic\textsuperscript{18,19}</td>
<td>4</td>
</tr>
<tr>
<td>Neurotoxic\textsuperscript{18,19}</td>
<td>4</td>
</tr>
<tr>
<td>Cytotoxic\textsuperscript{18,19}</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that borage had antigenadotrophic activity in rats\textsuperscript{23}.

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenadotrophic activity\textsuperscript{23}</td>
<td>4</td>
</tr>
</tbody>
</table>
A cross-sectional study was conducted on the effect of dietary supplementation of borage oil on the breast milk of atopic mothers\textsuperscript{24}. Twenty atopic mothers received borage oil for one week (230 mg or 460 mg of gamma-linolenic acid) while twenty 20 non-atopic mothers received a placebo\textsuperscript{24}. Arachidonic acid was found to be lower in breast milk of atopic mothers compared with non-atopic mothers\textsuperscript{24}. Supplementation of the atopic mothers with borage oil significantly increased the levels of gamma-linolenic acid and dihomo-gamma-linolenic acid in breast milk in a dose-related way, but the level of arachidonic acid was not increased\textsuperscript{24}. The authors did not report any adverse effects of borage oil supplementation on the mother or the infant\textsuperscript{24}.

Borage oil has been reported to contain small amounts of pyrrolizidine alkaloids\textsuperscript{20}. Pyrrolizidine alkaloids are hepatotoxic, pneumotoxic, genotoxic, neurotoxic and cytotoxic, and may cause hepatic veno-occlusive disease\textsuperscript{18, 19}.

**CONSTITUENTS**

Gamma-linolenic acid (GLA)\textsuperscript{15}
Pyrrolizidine alkaloids

PHARMACOLOGY

Diets rich in borage oil were shown to reduce systolic blood pressure, lower aldosterone, increase plasma renin and inhibit adrenal responsiveness to angiotensin II.

Borage oil alters stress reactivity in humans by attenuating blood pressure and heart rate responses to stress, increasing skin temperature, improving task performance and augment the arterial baroreflex control of vascular resistance.

The borage oil constituent GLA increases prostaglandin E levels and reduces T cell proliferation in vivo.

Borage oil reverses epidermal hyperproliferation.

GLA supplementation was shown to decrease plasma triglyceride, increase HDL-cholesterol, and significantly decrease total cholesterol and LDL-cholesterol.

GLA supplementation was shown to decrease platelet aggregation and increase bleeding time by 40%.

Borage oil supplementation does not improve insulin sensitivity in vivo.

DRUG INTERACTIONS

Anesthesia

Anti-convulsant/Anti-seizure Drugs

Anticoagulant/Antiplatelet Drugs

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Phenothiazines

PARTS USED

Seed and leaves
References


CALAMUS

*Acorus calamus*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**¹

Cinnamon sedge, gladdon, grass myrtle, myrtle flag, myrtle sedge, sweet cane, sweet cinnamon, sweet flag, sweet grass, sweet myrtle, sweet root, sweet rush, sweet sedge

**INDICATIONS**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract disorders, digestive stimulant²,³</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially hepatocarcinogenic⁴⁻⁸</td>
</tr>
</tbody>
</table>

Calamus contains beta-asarone, a volatile oil which has been shown to be hepatocarcinogenic in animal studies and in laboratory studies on human lymphocytes⁴⁻⁸.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue⁹</td>
</tr>
<tr>
<td>Potential abortifiacient⁹</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that calamus was an emmenagogue and a potential abortifiacient⁹.
LACTATION

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially hepatocarcinogenic(^4)(^{-8})</td>
</tr>
</tbody>
</table>

Calamus contains beta-asarone, a volatile oil which has been shown to be hepatocarcinogenic in animal studies and in laboratory studies on human lymphocytes\(^4\)\(^{-8}\).

CONSTITUENTS

Essential oils\(^5\)\(^,7\)\(^,8\)\(^,10\): alpha- and beta-asarone (volatile ethers)

TOXICOLOGY

LD50 of the tincture (1:2): 5 ml/kg\(^10\)

Dietary levels of 500-5,000 ppm of oil are carcinogenic in animals\(^10\)

PHARMACOLOGY

Beta-asarone is potentially hepatocarcinogenic\(^7\)\(^,8\). Once beta-asarone has undergone metabolic 1’-hydroxylation in the liver, its carcinogenic potency was reported as minimal where its major metabolite (2,4,5-trimethoxycinnamic acid) was not carcinogenic\(^7\)\(^,8\)\(^,11\).

Calamus oil inhibits monoamine oxidase (MAO) activity and stimulates D- and L-amino oxidase\(^12\).

Beta-asarone has antispasmodic activity in vitro in the tracheal, intestinal, uterine, bronchial and vascular smooth muscle\(^12\)\(^,13\).

Calamus has a sedative effect and potentiates the barbiturate effect (increased sleeping time, reduction in body temperature)\(^12\).

Alpha-asarone decreases LDL cholesterol and triglycerides and increases HDL\(^14\)\(^,15\).

Alpha-asarone is non-mutagenic in mice\(^16\).
DRUG INTERACTIONS

Anticoagulant drugs\textsuperscript{17}

MOAI drugs\textsuperscript{12}

Sedative/Barbiturate drugs\textsuperscript{12}

PARTS CONTAINING TOXINS\textsuperscript{10, 18}

Rhizome

References


CALENDULA

Calendula officinalis

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES\(^1\)

Garden marigold, gold-bloom, holligold, marigold, marybud, pot marigold

INDICATIONS

Topical

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns(^2)</td>
<td>B2</td>
</tr>
<tr>
<td>Acute otitis media (with \textit{Allium sativum}, \textit{Verbascum thapsus}, and \textit{Hypericum perforatum})(^3)</td>
<td>B2</td>
</tr>
<tr>
<td>Chronic colitis (with \textit{Taraxacum officinale}, \textit{Hypericum perforatum}, \textit{Melissa officinalis} and \textit{Foeniculum vulgare})(^4)</td>
<td>C</td>
</tr>
<tr>
<td>Wound healing(^5)</td>
<td>D</td>
</tr>
<tr>
<td>Skin inflammation(^6)</td>
<td>E</td>
</tr>
</tbody>
</table>

Homeopathic \textit{Calendula officinalis} (Calendula)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound healing(^7)</td>
<td>E</td>
</tr>
</tbody>
</table>
PREGNANCY

Oral

| Uterotonic effect\(^8\) | 3 |

Calendula was shown to have a uterotonic effect when applied to isolated rabbit and guinea pig uterine horn\(^8\).

| Potential abortifacient\(^9\) | 4 |
| Emmenagogue\(^9\) | 4 |
| Estrogenic\(^10\) | 4 |

A review article on the potential value of plants as sources of anti-fertility agents reported that calendula was a potential abortifacient and an emmenagogue, and that it had estrogenic activity\(^9, 10\).

| Spermatocide\(^1\) | 4 |
| Antiblastocyst\(^1\) | 4 |

A compendium on herb toxicology and drug interactions reported that when taken orally, calendula may have spermatocide and antiblastocyst activity\(^11\). Orally, calendula was not reported in the evidence-based medicine literature as having spermatocide or antiblastocyst activity.
**Topical**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Topically, calendula was not reported in the evidence-based medicine literature as being either safe or contraindicated during pregnancy.

**Homeopathic Calendula officinalis (Calendula)**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
</tr>
</tbody>
</table>

A homeopathic preparation of *Calendula officinalis*, called Calendula, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Homeopathic calendula is of minimal risk in pregnancy.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Calendula was not reported in the evidence-based medicine literature as being either safe or contraindicated during lactation.

**Homeopathic Calendula officinalis (Calendula)**

<table>
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<td>Minimal risk</td>
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A homeopathic preparation of *Calendula officinalis*, called Calendula, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Homeopathic calendula is of minimal risk in lactation.
CONSITUENTS

Faradiol esters\textsuperscript{12}

Triterpene alcohols\textsuperscript{13}: heliaol, taraxasterol, psi-taraxasterol, alpha-amyrin, beta-amyrin, lupeol, taraxerol, cycloartenol, 24-methyl-enecycloartanol, tirucalla-7,24-dienol and dammaradienol

Saponins\textsuperscript{14}

TOXICITY

LD\textsubscript{50} (intravenous)\textsuperscript{15}: 375mg/kg to 526mg/100g

LD\textsubscript{50} (sub-cutaneous)\textsuperscript{15}: 45mg/mouse

LD\textsubscript{100} (intraperitoneal)\textsuperscript{15}: 580mg/kg

PHARMACOLOGY

Calendula has anti-inflammatory and anti-edematous properties, where the faridol esters are believed to have the most pronounced anti-inflammatory effect\textsuperscript{6,12,16}.

Topically, the triterpene and flavonoid constituents were shown to have anti-inflammatory activity \textit{in vivo}\textsuperscript{6,13,16}.

Topically, calendula increases physiological regeneration and epithelization of surgical wounds\textsuperscript{17}.

Calendula may have immune stimulating activity \textit{in vitro}\textsuperscript{18}.

Calendula has antibacterial and antiviral activity\textsuperscript{19,20}.

Calendula has anti-mutagenic properties\textsuperscript{14}.

DRUG INTERACTIONS

Barbiturates\textsuperscript{21}

Drugs with Sedative Properties\textsuperscript{21}
PARTS USED

Flowers

REFERENCES


CHASTETREE

*Vitex agnus-castus*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Agnolyt, agnus castus, agnus-castus, chaste berry, chaste tree, chaste tree berry, chastetree, gattilier, hemp tree, monk's pepper, vitex, *Vitex agnus castus*

INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenstrual syndrome&lt;sup&gt;2-8&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Cyclic Mastalgia&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Hyperprolactinemia&lt;sup&gt;11&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Infertility&lt;sup&gt;5,12,13&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Acne&lt;sup&gt;5&lt;/sup&gt;</td>
<td>E</td>
</tr>
<tr>
<td>Menstrual disorders&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>E</td>
</tr>
<tr>
<td>Increases lactation&lt;sup&gt;5,12,14&lt;/sup&gt;</td>
<td>E</td>
</tr>
</tbody>
</table>

Homeopathic Preparation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility&lt;sup&gt;15&lt;/sup&gt;</td>
<td>B1</td>
</tr>
</tbody>
</table>

Pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue&lt;sup&gt;16&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>
A review article on the potential value of plants as sources of anti-fertility agents reported that chastetree was an emmenagogue\textsuperscript{17}.

<table>
<thead>
<tr>
<th>Uterine stimulant\textsuperscript{1}</th>
<th>4</th>
</tr>
</thead>
</table>

Compendia on drug interactions and safety and on natural products reported that chastetree is a uterine stimulant\textsuperscript{1}. There are no reports in the evidence-based literature of chastetree being a uterine stimulant or an emmenagogue.

<table>
<thead>
<tr>
<th>Prevention of miscarriages\textsuperscript{5}</th>
<th>4</th>
</tr>
</thead>
</table>

A compendium on herbal medicine reported that chastetree is used by some clinicians during the first trimester of pregnancy to prevent miscarriages in patients with progesterone deficiency\textsuperscript{5}. There are no reports in the evidence-based literature that chastetree prevents miscarriages.

<table>
<thead>
<tr>
<th>Hormonal activity\textsuperscript{18}</th>
<th>4</th>
</tr>
</thead>
</table>

Chastetree may have estrogenic and progesterone activity\textsuperscript{18}.

**Homeopathic Preparation**

<table>
<thead>
<tr>
<th>Increases progesterone\textsuperscript{15}</th>
<th>1a</th>
</tr>
</thead>
</table>

A prospective, randomized, placebo-controlled, double-blind study was conducted on a homeopathic preparation of chastetree for women with fertility disorders\textsuperscript{15}. The researchers observed a non-significant increase in fertility and a significant increase of progesterone during the luteal phase\textsuperscript{15}. 
LACTATION

<table>
<thead>
<tr>
<th>CONFLICTING EVIDENCE</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases lactation$^{5,12,14}$</td>
<td>4</td>
</tr>
<tr>
<td>Decreases lactation$^4$</td>
<td>4</td>
</tr>
</tbody>
</table>

Compendia on herbal medicine and a plant monograph report that chastetree increases lactation$^{5,12,14}$. Other sources report that chastetree decreases lactation as it suppresses prolactin release$^4$. There are no reports in the evidence-based literature of chastetree either increasing or decreasing lactation.

<table>
<thead>
<tr>
<th>Hormonal activity$^{18}$</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Chastetree may have estrogenic and progesterone activity$^{18}$.

**Homeopathic Preparation**

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<tr>
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</table>

A prospective, randomized, placebo-controlled, double-blind study was conducted on a homeopathic preparation of chastetree for women with fertility disorders$^{15}$. The researchers observed a non-significant increase in fertility and a significant increase of progesterone during the luteal phase$^{15}$.

**CONSTITUENTS$^1$**

Essential oils$^{14}$: limonene, cineol, pinene, and sabinene

Iridoid glycosides: aucubin and agnoside$^{5,19}$
Flavonoids: casticin, kaempferol, quercetagetin, orientin, and isovitexin\textsuperscript{5,14}.

Diterpenes: including vitexilactone, rotundifuran, and 6-beta,7 beta-diacetoxy-13-hydroxy-labda-8,14-dien\textsuperscript{12,14,19,20}.

Essential fatty acids: oleic acid, linolenic acid, palmitic acid, and stearic acid\textsuperscript{12}.

**TOXICITY**

No information available\textsuperscript{5}.

The LD\textsubscript{50} of *Vitex leucoxylon* leaf, same genus as chastetree, was >3000mg/kg (ethanol extract) and 800-1200mg/kg (cold aqueous infusion)\textsuperscript{21}.

**PHARMACOLOGY**

Chastetree may have estrogenic and progesterone activity\textsuperscript{18}.

Chastetree selectively binds to beta estrogen receptors (heart, vasculature, bone and bladder)\textsuperscript{22}.

Chastetree may affect dopamine, acetylcholine and opioid receptors\textsuperscript{20}.

In high doses, chastetree has agonist effects on pituitary dopamine (D2) receptors\textsuperscript{23,24}.

In women with hyperprolactinemia, chastetree appears to suppress prolactin release and normalize luteal phase defects in the menstrual cycle\textsuperscript{11}.

In men, lower doses of chastetree increase prolaction release while higher doses suppress prolaction release; chastetree does not appear to affect testosterone levels\textsuperscript{25}.

Chastetree may inhibit the growth of breast, ovarian, cervical, gastric, colon and lung cancer cells\textsuperscript{26,27}.

Chastetree essential oils have antibacterial and antifungal properties\textsuperscript{5}.

**DRUG INTERACTIONS**

Antipsychotic drugs\textsuperscript{23,24}.
Dopamine agonists\textsuperscript{20, 23, 24}

Oral contraceptives\textsuperscript{28}

Hormone replacement therapy\textsuperscript{28}

\textbf{PART USED}\textsuperscript{29}

Fruit

\section*{REFERENCES}


COFFEE

*Coffea arabica; C. canephora; C. robusta; C. liberica*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

CAFE, CAFFE, ESPRESSO, JAVA, MOCHA

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases mental alertness and performance</td>
<td>B1</td>
</tr>
<tr>
<td>Decreases risk of Parkinson’s disease</td>
<td>C</td>
</tr>
<tr>
<td>Decreases risk of symptomatic gallbladder disease in men</td>
<td>C</td>
</tr>
<tr>
<td>Decreases risk of gallstones in women</td>
<td>C</td>
</tr>
<tr>
<td>Rectal cancer prevention</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>1b</td>
</tr>
</tbody>
</table>

A case-control study of 3,149 pregnant women reported that serum paraxanthine, a caffeine metabolite, concentration was higher in the women who had spontaneous abortions than in the controls. Drinking more that 6 cups of coffee per day increases the risk of spontaneous abortions and that only extremely high serum paraxanthine concentrations are associated with spontaneous abortion.

A case-control study of 1,498 pregnant women reported that the consumption of 375 mg or more caffeine per day during pregnancy may increase the risk of spontaneous abortion.
<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of still birth&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>A prospective follow up study on 18,478 singleton pregnancies in women with valid information about coffee consumption during pregnancy&lt;sup&gt;11&lt;/sup&gt; reported that pregnant women who drink 8 or more cups of coffee per day have double the risk of stillbirth, when compared to women who do not drink coffee during pregnancy&lt;sup&gt;11&lt;/sup&gt;.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Level</td>
<td></td>
</tr>
<tr>
<td>Low birth weight infants&lt;sup&gt;12, 13&lt;/sup&gt;</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>A large prospective study on 2,291 mothers reported that women consuming more than 600 mg of caffeine per day are at greater risk for having low birth weight infants&lt;sup&gt;13&lt;/sup&gt;. A prospective study on 63 women reported that pregnant non-smokers consuming caffeine more than 300 mg/day had statistically significant lower weights of newborns and placentas (p &lt; 0.05)&lt;sup&gt;12&lt;/sup&gt;.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Level</td>
<td></td>
</tr>
<tr>
<td>Teratogenic compounds&lt;sup&gt;14-17&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated caffeine intake causes histopathologically teratogenic effects on newborn rat cornea&lt;sup&gt;14&lt;/sup&gt;. A study on the effects of coffee during pregnancy on mice reported long-term teratopharmacological and behavioral alterations in the offspring of pregnant mice that consumed coffee&lt;sup&gt;16&lt;/sup&gt;. A similar study on mice reported teratogenic effects associated with coffee ingestion during pregnancy&lt;sup&gt;17&lt;/sup&gt;. A review study, however, reported that when caffeine is administered in fractioned quantities during the day, as it is the case with human caffeine intake, caffeine is no longer a teratogen in animals&lt;sup&gt;18&lt;/sup&gt;.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Level</td>
<td></td>
</tr>
<tr>
<td>Impairs trace mineral absorption in fetus&lt;sup&gt;19&lt;/sup&gt;</td>
<td>3</td>
</tr>
</tbody>
</table>
A study on the effect of coffee consumption on pregnancy and lactation in mice\textsuperscript{19} reported that maternal coffee intake may impair mobilization of trace elements from liver reserves in early life and that this may result in reduced hemoglobin synthesis\textsuperscript{19}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmful to the fetus\textsuperscript{20}</td>
</tr>
<tr>
<td>Crosses the placenta\textsuperscript{20}</td>
</tr>
</tbody>
</table>

A compendium on the safety of drugs in pregnancy and lactation reported that over 3 cups of caffeine a day (300 mg) may be harmful to the fetus\textsuperscript{20}. The compendium also reported that caffeine crosses the human placenta where fetal blood and tissue levels are similar to maternal concentrations\textsuperscript{20}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>3 cups of coffee throughout the day – possibly safe\textsuperscript{21, 22}</td>
</tr>
</tbody>
</table>

A drug compendium and a review study reported that 3 cups of coffee (approximately 300 mg of caffeine) consumed throughout the day seems safe during pregnancy\textsuperscript{21, 22}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogenic\textsuperscript{23}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that coffee has estrogenic activity\textsuperscript{23}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Teratogenic compounds\textsuperscript{14-17}</td>
</tr>
</tbody>
</table>

Two studies reported teratogenic and behavioral alterations in animals whose mothers were fed coffee\textsuperscript{14, 16}. A similar study on mice reported teratogenic effects associated with coffee ingestion during pregnancy\textsuperscript{17}. Since caffeine appears in breast milk at half the concentration as in the
mother’s plasma, newborns may be exposed to teratogenic compounds\textsuperscript{24}. A review study, however, reported that when caffeine is administered in fractioned quantities during the day, as it is the case with human caffeine intake, caffeine is no longer a teratogen in animals\textsuperscript{18}.

<table>
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<tbody>
<tr>
<td>Impairs trace mineral absorption in newborn\textsuperscript{19}</td>
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</tbody>
</table>

A study on the effects of coffee consumption on pregnancy and lactation in mice reported that maternal coffee intake may impair mobilization of trace elements from liver reserves in early life and that this may result in reduced hemoglobin synthesis\textsuperscript{19}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause sleeping disorders\textsuperscript{25}</td>
</tr>
</tbody>
</table>

A compendium on herbal medicine reported that nursing mothers who consume caffeine may have infants with sleeping disorders\textsuperscript{25}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulates breast milk production\textsuperscript{22}</td>
</tr>
</tbody>
</table>

A review study reported that coffee consumption stimulates breast milk production in women and that it does not change breast milk composition\textsuperscript{22}.

**CONTRAINDICATIONS**

Cardiac problems\textsuperscript{15}

Kidney disease\textsuperscript{15}

Hyperthyroidism\textsuperscript{15}

**CAUTION**

People who have a predisposition to convulsion or anxiety should not drink more than 5 cups or 500 mg of caffeine per day\textsuperscript{15}. 
TOXIC CONSTITUENTS

Methylxanthine alkaloid: caffeine

Polyphenolic acid: chlorogenic acid

Caffeol

Diterpenes

TOXICITY

Toxic dose of caffeine: 1 g

Lethal dose of caffeine: 10 g (adult) and 5.3 g (child)

PHARMACOLOGY

Caffeine is a powerful stimulant of the central nervous system, respiration and skeletal muscles.

Caffeine causes cardiac stimulation, coronary dilation, smooth muscle relaxation, increases blood pressure, increases heart rate and contractility, and diuresis.

Coffee stimulates gastric secretions.

Caffeine crosses the human placenta where fetal blood and tissue levels are similar to maternal concentrations.

Chlorogenic acid, a constituent in coffee, is reported to have stimulant, diuretic, choleretic properties and allergenic properties.

Chlorogenic acid may raise homocysteine levels.

Cafestol, a diterpene in unfiltered coffee, was shown to raise plasma triacylglycerol levels in humans.

Caffeine has antiplatelet activity.
DRUG INTERACTIONS

Acetaminophen\(^3\)\(^4\)

Alendronate\(^3\)\(^5\)

Anticoagulant/Antiplatelet Drugs\(^3\)\(^2\), \(^3\)\(^3\)

Anti-diabetic drugs\(^3\)\(^4\)

Aspirin\(^3\)\(^2\), \(^3\)\(^3\), \(^3\)\(^6\)

Benzodiazepines\(^3\)\(^5\)

Beta-adrenergic agonists\(^3\)\(^7\)

Cimetidine\(^3\)\(^5\)

Clozapine\(^3\)\(^8\)

CNS stimulants\(^3\)\(^9\), \(^4\)\(^0\)

Disulfiram\(^3\)\(^7\)

Ephedrine\(^3\)\(^4\), \(^4\)\(^1\)

Ergotamine\(^3\)\(^7\)

Estrogen\(^4\)\(^2\)

Lithium\(^4\)\(^3\), \(^4\)\(^4\)

Mexiletine\(^3\)\(^5\)

Monoamine oxidase inhibitors (MAOIs)\(^3\)\(^4\)

Oral contraceptives\(^3\)\(^5\)

Phenylpropanolamine\(^3\)\(^5\)
Quinolones\textsuperscript{45-47}  
Riluzole\textsuperscript{35}  
Terbinafine\textsuperscript{35}  
Theophylline\textsuperscript{35}  
Verapamil\textsuperscript{35}  

\textbf{PARTS USED}\textsuperscript{15}  
Dried ripe seed  

\textbf{References}  


CRANBERRY

_Vaccinium macrocarpon, V. oxycoccos_

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

American cranberry, arandano Americano, arandano trepador, cranberries, European cranberry, grosse moosbeere, kranbeere, large cranberry, moosebeere, mossberry, ronce d'Amerique, small cranberry, trailing swamp cranberry, tsuru-kokemomo

INDICATIONS

Extract

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of urinary tract infections&lt;sup&gt;2-4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A systematic review concluded that the small number of poor quality trials gives no reliable evidence of the effectiveness of cranberry juice for the prevention of urinary tract infections<sup>2</sup>. The systematic review also reported that other cranberry products such as cranberry capsules may be more acceptable<sup>2</sup>.

Juice

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of urinary tract infections&lt;sup&gt;5-6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urinary tract infections&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Periodontal disease&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A systematic review concluded that the small number of poor quality trials gives no reliable evidence of the effectiveness of cranberry juice for the prevention of urinary tract infections<sup>2</sup>. The 2 studies above were not included in the systematic review<sup>5,6</sup>. 
PREGNANCY

<table>
<thead>
<tr>
<th>Grade</th>
<th>Commonly used\textsuperscript{10, 11}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Safety Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

A survey was conducted on 400 Norwegian postpartum women\textsuperscript{11}. The authors reported that cranberry was one of the most commonly used herbs during pregnancy, mostly for urinary tract infections\textsuperscript{11}. This study did not evaluate the safety of cranberry during pregnancy\textsuperscript{11}. There are no reports in the evidence-based medicine literature of cranberry being either safe or contraindication during pregnancy.

Food

<table>
<thead>
<tr>
<th>Grade</th>
<th>Minimal risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal compendium reported that cranberry is of minimal risk during pregnancy when consumed in food quantities\textsuperscript{12}.

LACTATION

<table>
<thead>
<tr>
<th>Grade</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based medicine literature of cranberry being either safe or contraindication during lactation.

Food

<table>
<thead>
<tr>
<th>Grade</th>
<th>Minimal risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
A herbal compendium reported that cranberry is of minimal risk when consumed in food quantities\textsuperscript{12}.

**CAUTION**

Kidney stones\textsuperscript{13}

**CONSTITUENTS\textsuperscript{14}**

Proanthocyanidins

Triterpenoids

Lectins

Catechins

Ascorbic acid

Benzoic acid

Quinic acid

Citric acid

Malic acid

**TOXICITY**

Consuming up to 4L/day of cranberry juice was shown to be non-toxic in healthy individuals\textsuperscript{15}.

Ingesting large amounts of cranberry juice (>3L/day) may result in diarrhea, gastrointestinal distress, other gastrointestinal symptoms or toxicity in infants or young children\textsuperscript{16-18}.

**PHARMACOLOGY**

The proanthocyanidins in cranberry interfere with bacterial adherence to the urinary tract epithelial cells\textsuperscript{19-27}.
In the case of *Escherichia coli* (*E. coli*), the cause of most urinary tract infections (UTIs), proanthocyanidins were shown to wrap around these bacteria and prevent their adherence to the urinary tract wall\textsuperscript{7,28,29}.

Cranberry juice cocktail was shown to inhibit adherence in 77 clinical isolates of *Escherichia coli* obtained from patients with diagnosed urinary tract infections and anti-adherence activity against Gram-negative rods\textsuperscript{7}.

The fructose in cranberries was shown to contribute to the antibacterial activity of cranberry\textsuperscript{25,29,30}.

Cranberry does not appear to have the ability to dislodge bacteria that are already adhered to the urinary tract epithelial cells\textsuperscript{31}.

Cranberry juice was shown to have antibacterial activity against *E. coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Proteus mirabilis*\textsuperscript{7,24,29}.

Cranberry was shown to have antiviral action against the poliovirus type 1\textsuperscript{32}.

Cranberry may prevent the adherence of *Helicobacter pylori* in the stomach\textsuperscript{28}.

Cranberry may prevent adhesion of plaque bacteria that cause periodontal disease\textsuperscript{9}.

Cranberry may have antioxidant and anticarcinogenic activity\textsuperscript{33,34}.

**DRUG INTERACTIONS\textsuperscript{1}**

Warfarin\textsuperscript{35,36}.

Drugs metabolized by cytochrome P450 2C9\textsuperscript{35,36}.

**PART USED**

Fruit\textsuperscript{1}
REFERENCES


DAMIANA

*Turnera aphrodisiaca*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

*Damiana aphrodisiaca*, damiana herb, damiana leaf, herba de la pastora, Mexican damiana, mizibcoc, old woman's broom, rosemary, *Turnerae diffusae folium*, *Turnerae diffusae herba*

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sexual dysfunction (with ginseng, ginkgo, L-arginine, multivitamins and minerals)(^2)</td>
<td>B1</td>
</tr>
<tr>
<td>Weight loss (with yerbe mate and guarana)(^3)</td>
<td>B2</td>
</tr>
<tr>
<td>Sexual dysfunction(^4, 5)</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant(^6)</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that herbs from the *Turnera sp.*, including damiana, are uterine stimulants\(^6\).

LACTATION

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of damiana being either safe or contraindicated during lactation.
CONSTITUENTS

Arbutin

Flavonoids

Flavone glycosides

TOXICITY

An individual exhibited tetanus-like convulsions and paroxysms, similar to those of rabies or strychnine poisoning, following the ingestion of approximately 200g of damiana.

High doses of arbutin (1 g) are considered toxic - 100 g of damiana plant material would have to be consumed to equal a dose of 1 g of arbutin.

PHARMACOLOGY

Damiana contains high levels of phyto-progestins, which may increase the progestin activity of saliva.

Progesterone-binding herbs, such as damiana, were shown to have neutral or antagonist effects on breast cancer cell lines.

Damiana extracts are reported to have CNS depressant activity.

Damiana was shown not to have hypoglycemic effects.

Arbutin may have antibacterial properties.

DRUG INTERACTIONS

Diabetic drugs (when using non-water extract or whole herb)

PARTS USED

Leaf and stem
REFERENCES


DANDELION

*Taraxacum officinale*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Blowball, cankerwort, common dandelion, dandelion herb, dandelion root, lion's tooth, pissenlit, priest's crown, swine snout, *Taraxaci herba*, taraxacum, wild endive.

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (multiple herb combination Jiedu Yanggan Gao)²</td>
<td>B2</td>
</tr>
<tr>
<td>Urinary tract infections (with uva ursi)³</td>
<td>C</td>
</tr>
<tr>
<td>Non-specific colitis (with St. John’s wort, lemon balm, calendula and fennel)⁴</td>
<td>C</td>
</tr>
<tr>
<td>Diabetes⁵</td>
<td>E</td>
</tr>
<tr>
<td>Anti-inflammatory effects⁶</td>
<td>E</td>
</tr>
<tr>
<td>Diuretic⁷</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of dandelion being either safe or contraindicated during pregnancy.
Food amounts

<table>
<thead>
<tr>
<th>Minimal risk&lt;sup&gt;8&lt;/sup&gt;</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal medicine compendium reported that dandelion is of minimal risk during pregnancy when consumed in food amounts<sup>8</sup>.

LACTATION

<table>
<thead>
<tr>
<th>Unknown</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of dandelion being either safe or contraindicated during lactation.

CAUTION

Bile duct and intestinal obstruction<sup>9</sup>

Kidney disease<sup>9</sup>

CONSTITUENTS

Root

Eudesmanolide and germacranelide sesquiterpene lactones<sup>10</sup>

Triterpene alcohols and phytosterols<sup>10, 11</sup>

Gamma-butyrolactone glycoside<sup>12</sup>: taraxacoside

Caffeic acid and p-hydroxyphenylacetic acid<sup>13</sup>

Potassium<sup>14</sup>

Inulin<sup>14, 15</sup>
Leaf

Germacranolide sesquiterpene lactones\textsuperscript{10, 16}

Triterpenes\textsuperscript{17}: cycloartenol

Phytosterols\textsuperscript{16, 17}

p-hydroxyphenylacetic acid\textsuperscript{10, 16}

Flavonoids\textsuperscript{15}: apigenin-7-glucoside, luteolin-7-glucoside

Furan fatty acids\textsuperscript{18}

Potassium\textsuperscript{19-21}

\textbf{TOXICITY}

Root

LD\textsubscript{50} (intraperitoneally): 36.6 g/kg\textsuperscript{19}

\textbf{Aboveground parts}

LD\textsubscript{50} (intraperitoneally): 28.8 g/kg\textsuperscript{19}.

\textbf{PHARMACOLOGY}

The bitter constituents in dandelion root increase bile flow\textsuperscript{22}.

Dandelion was shown to have diuretic and anti-inflammatory effects\textsuperscript{8}.

Dandelion may have some hypoglycemic activity\textsuperscript{8}.

The constituent taraxacin (eudesmanolides) is an appetite stimulant\textsuperscript{23}.

Dandelion may have a mild laxative effect\textsuperscript{24}.

Dandelion has been shown to have antitumor activity \textit{in vitro}\textsuperscript{8}. 
DRUG INTERACTIONS

Antacids
Anti-diabetic drugs
H₂-blockers
Lithium
Potassium-sparing diuretics
Proton pump inhibitors

PARTS USED

Whole plant

References


DEADLY NIGHTSHADE

*Atropa belladonna*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Belladonna, dwale, devil’s cherries, poison black cherry, devil's herb, divale, dwayberry, great morel, naughty man's cherries

INDICATIONS

*Atropa belladonna* Herbal or Pharmaceutical Preparations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable Bowel Syndrome(^2,3) (in combination with other drugs)</td>
<td>B1</td>
</tr>
<tr>
<td>Migraine Headaches(^4,5) (in combination with other drugs)</td>
<td>B1</td>
</tr>
<tr>
<td>Premenstrual Syndrome(^6)</td>
<td>B1</td>
</tr>
<tr>
<td>Autonomic Nervous system conditions(^7,8)</td>
<td>B2</td>
</tr>
<tr>
<td>Airway obstruction(^9)</td>
<td>C</td>
</tr>
</tbody>
</table>

Homeopathic *Atropa belladonna* (Belladonna)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine headaches(^10)</td>
<td>B1</td>
</tr>
<tr>
<td>Otitis media(^11)</td>
<td>C</td>
</tr>
</tbody>
</table>
PREGNANCY

<table>
<thead>
<tr>
<th>Drug derivative - Minimal Side-Effects during Labour\textsuperscript{12, 13}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
</tr>
</tbody>
</table>

Drugs derived from *Atropa* are sometimes used during labour or abortions\textsuperscript{12, 13}. Prininium bromide, an atropine drug, was administered to women in labour as part of a controlled trial\textsuperscript{12}. The atropine administered lead to a shorter period of labour, normal intra-partum hemorrhage and normal amniotic fluid\textsuperscript{12}. The atropine had no effect on fetal heart rate or AGPAR score\textsuperscript{12}.

<table>
<thead>
<tr>
<th>Teratogenic - Potential Birth Defects\textsuperscript{14, 15}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Teratogenic - Potential eye malformation\textsuperscript{16}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Teratogenic - Potential respiratory abnormalities\textsuperscript{17}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Teratogenic - Potential penile abnormalities (hypospadia)\textsuperscript{17}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Teratogenic - Potential ear malformations\textsuperscript{17}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Although no direct relationship between first trimester use of atropine and birth defects was found, a study reported an increase in birth defects in the offspring of mothers who had taken belladonna\textsuperscript{14}. Scopolamine and hyoscyamine were found to have teratogenic effects in animals\textsuperscript{15}. The eyes of atropine-exposed chicken embryos were found to have abnormal features and appearance\textsuperscript{16}. An evidenced-based compendium on natural health products reported that there is anecdotal reports that the use of belladonna during pregnancy may increase the risk of respiratory abnormalities, hypospadias (penile urethral malformation in males) and ear malformations\textsuperscript{17}.

<table>
<thead>
<tr>
<th>No adverse effect with phenothiazine – First Trimester\textsuperscript{18}</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
A case report in the scientific literature reported that belladonna supplementation, along with phenothiazine, to two pregnant women with sialorrhea and hyperemesis resulted in no side effects to the women or to the newborn\textsuperscript{18}.

| Temporary mydriasis\textsuperscript{19} | 2 |

A neonate whose mother had recently taken the antidepressant amitriptyline developed fixed dilated pupils after a modest dose of intravenous atropine\textsuperscript{19}. The neonate's pupils became reactive again after 7 hours and there were no neurological sequelae\textsuperscript{19}.

**Homeopathic *Atropa belladonna* (Belladonna)**

| Minimal Risk\textsuperscript{20, 21} | 1a |

A homeopathic preparation of *Atropa belladonna*, called Belladonna, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. A randomized controlled trial found that Belladonna did not produce any significant symptoms that were different to placebo\textsuperscript{20}.

**LACTATION**

| Potentially unsafe - Caution\textsuperscript{1} | 4 |

A compendium on natural health products reported that *Atropa* decreases the production of breast milk due to its anticholinergic properties and that it is secreted in breast milk\textsuperscript{1}. *Atropa* was not reported in the evidence-based literature as either being safe or causing harm to the nursing infant.

**CONTRAINDICATIONS**

Glaucoma\textsuperscript{22}
CONSTITUENTS

Alkaloids\textsuperscript{22}: Atropine (hyoscyamine), scopolamine (hyoscine)

TOXICOLOGY

Lethal dose (children): 10-100 mg of atropine, 5-50 g of powdered Deadly nightshade, more than 3 berries\textsuperscript{22}

PHARMACOLOGY

Atropine acts on the muscarinic receptors where it blocks the parasympathetic effects on smooth muscle, cardiac muscle and glandular cells\textsuperscript{23}.

Atropine blocks the activity of the vagus nerve, thereby increasing the firing rate of the sinoatrial node\textsuperscript{23}.

Atropine reduces heart rate and peristalsis, increases bladder pressure, relaxes the bile duct, reduces the production of saliva and gastric fluids, and reduces the secretions from the pancreas, eye and bronchi\textsuperscript{23}.

Deadly nightshade is believed to have no or very little effect on blood pressure control\textsuperscript{7}.

DRUG INTERACTIONS

Anticholinergic Drugs\textsuperscript{24}

PARTS CONTAINING TOXINS\textsuperscript{22}

Roots, leaves, berries, flowers

REFERENCES


**DONG QUAI**

*Angelica sinensis*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**

Chinese angelica, dang gui, danggui, dong qua, dong-quai, ligustilides, phytoestrogen, tan kue bai zhi, tang kuei

**INDICATIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenstrual syndrome (within a multiple herb Chinese formula)</td>
<td>A</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>B2</td>
</tr>
<tr>
<td>Pulmonary hypertension in patients with chronic obstructive pulmonary disease (COPD) (with nifedipine)</td>
<td>B2</td>
</tr>
<tr>
<td>Cerebral thrombosis (within a multiple herb Chinese formula)</td>
<td>C</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>C</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>C</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura (within a multiple herb Chinese formula)</td>
<td>D</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No estrogenic effects</td>
<td>1a</td>
</tr>
</tbody>
</table>
A randomized placebo controlled trial on post-menopausal women was conducted in order to evaluate the estrogenic effects of dong quai\(^9\). They concluded that dong quai does not produce estrogen-like responses in endometrial thickness or in vaginal maturation and that it was no more helpful than placebo in relieving menopausal symptoms\(^9\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant(^{10,11})</td>
</tr>
<tr>
<td>Uterine relaxant(^{10,12})</td>
</tr>
</tbody>
</table>

In mice, decoctions of Dong Quai were found to have a stimulating effect on the uterus \textit{in vitro}\(^{11}\). The stimulating action of Dong Quai was related to its stimulation of H1-receptors in the uterus\(^{11}\). Ferulic acid, a constituent of dong quai, was found to inhibit uterine contraction in rats\(^{12}\).

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Dong quai was not reported in the evidence-based medicine literature as being contraindicated in lactation.

**CONTRAINDICATIONS**

Warfarin therapy\(^{13,14}\)

**CAUTION**

Menorrhagia

Metrorrhagia

**CONSTITUENTS\(^1,12,15\)**

Coumarins: osthola, psoralen, bergapten
Butylidene phthalide
Ligustilide
n-butylidene-phthalide
Sesquiterpenes
Carvacrol
Dihydrophthalic anhydride
Ferulic acid

PHARMACOLOGY

Dong quai has anti-inflammatory effects where it lowered plasma prostaglandin F2 alpha (PGF2 alpha) and menstrual blood PGF2 alpha in patients with dysmenorrhea\(^6\).

Dong quai was found to stimulate the growth of human breast cancer cell lines independently of estrogenic activity\(^7\).

The coumarin constituent bergapten is believed to be carcinogenic\(^1\).

The coumarin constituent osthol has a stimulant effect on the central nervous system\(^1\).

Dong quai appears to potentiate the effect of warfarin and thereby increase prothrombin time\(^12, 14, 18, 19\).

Intravenous administration of dong quai decreased serum gastrin levels of inferior vena cava, hepatic and peripheral veins in patients with liver cirrhosis\(^6\).

Dong quai has an analgesic and antiseptic effect in abdominal pain\(^3\).

Dong quai administered with nifedipine was shown to decrease mean pulmonary arterial pressure and increase cardiac output and PaO2 in COPD\(^4\).

In combination with ginseng and astragalus, dong quai was found to improve many symptoms of coronary artery disease\(^7\).
The coumarins psoralen and bergapten are photosensitizing and may cause photodermatitis\textsuperscript{1}.

**DRUGS INTERACTIONS**

Anti-coagulant/anti-platelet drugs\textsuperscript{1}

Warfarin\textsuperscript{13, 14, 18, 19}

**PARTS USED**\textsuperscript{10}

Root

**REFERENCES**


ECHINACEA

_Echinacea angustifolia, E. pallida, E. purpurea_

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

American cone flower, black Sampson, black Susan, _Brauneria angustifolia, Brauneria pallida_, comb flower, coneflower, echinacea wurzel, hedgehog, igelkopfwurzel, Indian head, Kansas snakeroof, narrow-leaved purple cone flower, pale coneflower, purple cone flower, purpursonnenhutkraut, purpursonnenhutwurzel, racine d'echininacea, red sunflower, rock-up-hat, roter sonnenhut, schmallblaettige kegelblumenwurzel, schmallblaettriger sonnenhut, scurvy root, snakeroof, sonnenhutwurzel

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection - Treatment</td>
<td>A</td>
</tr>
<tr>
<td>Radiation associated leukopenia</td>
<td>B2</td>
</tr>
<tr>
<td>Cancer survival time</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Risk</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
<td>1b</td>
</tr>
</tbody>
</table>

A prospective follow-up study on 206 pregnant women, 112 of which had used echinacea in the first trimester of pregnancy reported that gestational use of echinacea during the first trimester (organogenesis) is not associated with an increased risk for major malformations. The German Commission E compendium, produced by an expert panel on botanical medicine, considers oral...
Echinacea in recommended doses safe for use during pregnancy\textsuperscript{14}. Echinacea was not reported in the evidence-based literature as being contraindicated during pregnancy.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{14}</td>
</tr>
</tbody>
</table>

The German Commission E compendium, produced by an expert panel on botanical medicine, considers oral echinacea in recommended doses safe for use during lactation\textsuperscript{14}. Echinacea was not reported in the evidence-based medicine literature as being either safe or contraindicated during lactation.

**CONSTITUENTS\textsuperscript{15}**

Caffeic acid derivatives: echinocoside, cichoric acid, cynarin

Polysaccharides

Glycoproteins

Alkamides

**TOXICITY**

LD\textsubscript{50} in mice: >2500 mg/kg\textsuperscript{16}

LD\textsubscript{50} of intravenous echinacea juice: 50 mL/kg\textsuperscript{17}.

**PHARMACOLOGY**

The immune-stimulating properties have Echinacea have not been attributed to any single compound\textsuperscript{18}.

Echinacea increases the proliferation of phagocytes in spleen and bone marrow, stimulates monocytes to produce cytokines (IL-1, IL-6, TNF), increases the number of PMN, activates macrophages and promotes the adherence of PMN to endothelial cells\textsuperscript{19-22}. 
Echinacea was shown to inhibit hyaluronidase production in vitro and in vivo\textsuperscript{18, 23, 24}.

Echinacea has anti-viral, anti-bacterial and anti-fungal properties\textsuperscript{15, 25-27}.

Echinacea was shown to inhibit the influenza virus and the herpes simplex virus (I and II)\textsuperscript{26, 27}.

Topically, Echinacea has anti-inflammatory properties where it inhibits edema\textsuperscript{28, 29}.

Echinacea may interfere with cytochrome P450 (CYP) 3A4 (CYP3A4) enzyme\textsuperscript{30}.

**DRUG INTERACTIONS**

Immunosuppressant drugs\textsuperscript{31}

Drugs metabolized by the cytochrome P450 (CYP) 3A4 (CYP3A4) enzyme\textsuperscript{30}

**PARTS USED\textsuperscript{32}**

Roots, stems and leaves

**REFERENCES**


EPHEDRA

*Ephedra vulgaris, E. distachya, E. equisetina, E. shennungiana, E. gerardiana, E. intermedia, E. sinica*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Cao mahuang, Chinese ephedra, Chinese joint-fir, cao ma-huang, desert herb, *Ephedrae herba*, *Ephedra sinensis*, herbal ecstasy, Indian jointfir, joint fir, mahuang, ma huang, ma-huang, mahuanggen (ma huang root), Mongolian ephedra, muzei ma huang, Pakistani ephedra, popotillo, sea grape, shuang sui ma huang, teamster's tea, yellow astringent, yellow horse, zhong mahuang

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension during spinal anesthesia for cesarean delivery</td>
<td>A</td>
</tr>
<tr>
<td>Weight loss (with caffeine)</td>
<td>B1</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>B1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>B2</td>
</tr>
<tr>
<td>Asthmatic bronchoconstriction</td>
<td>B2</td>
</tr>
<tr>
<td>Hypotension (with caffeine)</td>
<td>B2</td>
</tr>
<tr>
<td>Sexual arousal in women</td>
<td>B2</td>
</tr>
<tr>
<td>Hypotension during epidural block</td>
<td>C</td>
</tr>
</tbody>
</table>
PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses the placenta</td>
</tr>
<tr>
<td>Does not affect fetal well-being or neonatal outcome</td>
</tr>
</tbody>
</table>

A randomized controlled trial on 40 pregnant women undergoing elective caesarian reported that ephedrine crosses the placenta where the fetal blood level is approximately 70% of the maternal level. The presence of ephedrine in the fetal circulation did not seem to have any deleterious effects on fetal well-being or neonatal outcome.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases neonatal heart rate</td>
</tr>
</tbody>
</table>

A study of fetal heart rate changes during epidural anesthesia in 71 patients found that ephedrine administration was associated with significant increases in fetal hear rate and beat-to-beat variability. The authors reported that the fetal heart rate changes were dose related and were not associated with fetal asphyxia as judged by measurement of fetal scalp blood pH or Apgar scores. A randomized controlled trial on 40 pregnant women undergoing elective caesarian reported that ephedrine increased fetal heart rate for 40 to 50 minutes after intramuscular injection to the mother. Ephedrine did not adversely affect the fetus.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that ephedra is a uterine stimulant and that its constituents ephedrine and pseudoephedrine are uterine stimulants.
### Ephedrine

<table>
<thead>
<tr>
<th>Level</th>
<th>May cause hypertension in the mother\textsuperscript{17,18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
</tr>
</tbody>
</table>

A systematic review on the dose-response characteristics of prophylactic IV ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery found that at larger doses of ephedrine, the likelihood of causing hypertension was actually more than that of preventing hypotension and there was also a minor decrease in umbilical arterial pH\textsuperscript{17}. As such, the authors did not recommend prophylactic ephedrine\textsuperscript{17}. A previous systematic review in 2002 also found similar results\textsuperscript{18}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Increases blood flow to the uterus\textsuperscript{19}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td></td>
</tr>
</tbody>
</table>

An outcome study in order to assess the effects of ephedrine on uterine artery velocities and resistance index using the Doppler technique during the active phase of labor found that a bolus administration of intravenous ephedrine may increase uterine perfusion pressure during labor and restore uterine blood flow to the placenta during uterine contractions; thereby preventing fetal asphyxia\textsuperscript{19}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Teratogenic – limb defects (with theophylline and phenobarbitol)\textsuperscript{20}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Two cases were observed of severe limb defects in infants following the use of sympathomimetic drugs during pregnancy\textsuperscript{20}. The mother of one infant had taken large doses of Primatene (ephedrine, theophylline, phenobarbital) as tablets and mist throughout pregnancy, where her baby was born with oligoectrosyndactyly\textsuperscript{20}. The authors also reported that studies in pregnant rabbits using Primatene in both low and high dosage resulted in limb reduction defects and other malformations in a significant number of the offspring compared with controls\textsuperscript{20}. 
A case was reported of an aborted human embryo from a mother who had taken four tablets of Tedral (130 mg theophylline, 25 mg ephedrine, 8 mg phenobarbital) for an upper respiratory tract infection when the embryo was at approximately 30 days of development\textsuperscript{21}.

A review study on the influence of epidural analgesia on fetal and neonatal well-being reported that epidural analgesia-containing ephedrine should be avoid in women with pregnancy-induced hypertension\textsuperscript{22}.

A review article on the potential value of plants as sources of anti-fertility agents reported that ephedrine is a uterine stimulant\textsuperscript{16}.

\textbf{Pseudoephedrine}

A retrospective cohort study was conducted on the relationship between maternal use of cough/cold/analgesic medications containing pseudoephedrine and risks of gastroschisis and small intestine atresia (SIA)\textsuperscript{23-25}. The authors examined the mothers of 206 gastroschisis cases, 126 SIA cases, and 798 controls\textsuperscript{23}. The risk of gastroschisis was elevated for use of pseudoephedrine and pseudoephedrine combined with acetaminophen\textsuperscript{23}. The risk of SIA was increased for use of pseudoephedrine and for use of pseudoephedrine in combination with acetaminophen\textsuperscript{23}.
A case-control study of gastroschisis where they evaluated the risks associated with mother's first-trimester use of medications found an elevated risk of gastroschisis with maternal use of pseudoephedrine\textsuperscript{24}. Another study found the same association between pseudoephedrine use during pregnancy and the increased risk of gastroschisis\textsuperscript{25}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratogenic – limb defects (with phenylephrine and phenylpropanolamine)\textsuperscript{20}</td>
</tr>
</tbody>
</table>

Two cases were observed cases of severe limb defects in infants following the use of sympathomimetic drugs during pregnancy\textsuperscript{20}. The mother of one infant had Triaminic (pseudoephedrine, phenylephrine, phenylpropanolamine) where her baby was born with distal limb defects\textsuperscript{20}.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant\textsuperscript{16}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that pseudoephedrine is a uterine stimulant\textsuperscript{16}.

**LACTATION**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cross into breast milk\textsuperscript{26}</td>
</tr>
</tbody>
</table>

A case was reported of a 3 month-old child with irritability, excessive crying and disturbed sleep patterns for 5 days\textsuperscript{26}. Further investigation led to the discovery that the mother was taking a long-acting nasal decongestant, containing dextrompheniramine and d-isoephedrine, for allergic rhinitis\textsuperscript{26}. Symptoms subsided after the mother discontinued the decongestant\textsuperscript{26}. The author reported that it was not possible to prove conclusively that ephedrine (d-isoephedrine) crosses into breast milk\textsuperscript{26}.
**Pseudoephedrine**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases milk production(^{27})</td>
</tr>
<tr>
<td>Unlikely to affect the infant(^{27})</td>
</tr>
</tbody>
</table>

A randomized crossover study was conducted on eight lactating women to assess the effects of pseudoephedrine on breast blood flow, temperature and milk production, and to estimate the likely infant dose during breastfeeding\(^{27}\). Pseudoephedrine was found to significantly reduced milk production, where the depression of prolactin secretion may be a contributing factor\(^{27}\). The authors reported that at the maximum recommended pseudoephedrine doses, the calculated infant dose delivered via milk was < 10% of the maternal dose, and is unlikely to affect the infant adversely\(^{27}\).

**CONTRAINDICATIONS**

Pregnancy induced hypertension\(^{32}\)

Enlarged prostate\(^{28}\)

Organic heart disease\(^{28}\)

Hypertension\(^{28}\)

Diabetes\(^{28}\)

Anxiety/restlessness\(^{28}\)

Closed-angle glaucoma\(^{28}\)

Impaired cerebral circulation\(^{28}\)

Phreochromocytoma\(^{28}\)

Hyperthyroidism\(^{28}\)
CAUTION

Anorexia

Insomnia

Suicidal persons

Concomitant use with caffeine

CONSTITUENTS

Alkaloids: ephedrine, pseudoephedrine, phenylpropanolamine, norpseudoephedrine, methylephedrine, norephedrine

TOXICITY

Ephedrine is toxic > 300 mg per day.

Lethal dose: 1-2 grams of ephedrine.

In dogs, the minimum dose at which death was reported was 5.8 mg/kg (2.6 mg/lb).

PHARMACOLOGY

Ephedrine decreases direct uterine arterial vasoconstriction during pregnancy by increasing the release of an endogenous vasodilator (nitrous oxide), either from the vascular endothelium or the vessel wall.

Ephedrine can stimulate uterine contractions, and theoretically, can be catabolized to mutagenic nitrosamines.

The sympathomimetics ephedrine and pseudoephedrine can directly and indirectly stimulate the sympathetic nervous system.

Ephedra alkaloids have been linked to myocarditis, myocardial infarction, coronary artery vasoconstriction, cardiac arrhythmia, cerebral hemorrhage, cerebral vasculitis and ischemic stroke.
Ephedrine and pseudoephedrine can increase systolic and diastolic blood pressure, heart rate and cardiac contractility, and cause peripheral vasoconstriction, bronchodilation and central nervous system stimulation.\(^3\)

Ephedrine causes thermogenesis and modest weight loss, possibly by stimulating norepinephrine release.\(^3\)

Ephedrine appears to have antitussive, bacteriostatic and anti-inflammatory properties.\(^3\),\(^\text{34},\)\(^\text{35},\)\(^\text{36},\)

Ephedrine may exacerbate urinary retention, but can also have diuretic effects.\(^4\)

Ephedrine relaxes the smooth muscle in the gastrointestinal and urinary tract.\(^4\)

Ephedrine causes catecholamine release and increases CNS stimulation, which may lead to better anaerobic exercise performance.\(^5\)

**DRUG INTERACTIONS**

Caffeine.\(^6\)

Dexamethasone (Decadron).\(^7\)

Diabetic drugs.\(^7\)

Ergotamine.\(^7\)

Monoamine oxidase inhibitors (MAOI).\(^7\)

Oxytocin.\(^7\)

QT-interval prolonging drugs.\(^7\)

Reserpine.\(^7\)

Theophylline.\(^7\)

Urinary acidifiers.\(^7\)

Urinary alkalinizers.\(^7\)
**PARTS USED**

Stems, twigs; root and fruits (lesser extent)

**REFERENCES**


**EVENING PRIMROSE**

*Oenothera biennis*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**

EPO, fever plant, huile d'onagre, king's cureall, night willow-herb, primrose, scabish, sun drop

**INDICATIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic Dermatitis and Eczema</td>
<td>A</td>
</tr>
<tr>
<td>Diabetic peripheral neuropathy</td>
<td>B1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>B1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>B2</td>
</tr>
<tr>
<td>Breast cysts</td>
<td>B2</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension and Pre-eclampsia</td>
<td>B2</td>
</tr>
<tr>
<td>Raynaud’s Phenomenon</td>
<td>B2</td>
</tr>
<tr>
<td>Post-viral fatigue syndrome</td>
<td>B2</td>
</tr>
<tr>
<td>Breast cancer (with tamoxifen)</td>
<td>B2</td>
</tr>
<tr>
<td>Breast pain (mastalgia)</td>
<td>C</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>C</td>
</tr>
<tr>
<td>Premenstrual syndrome</td>
<td>E</td>
</tr>
</tbody>
</table>
PREGNANCY

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{10-12,19,20}</td>
</tr>
</tbody>
</table>

A randomized controlled trial was conducted on the effects of evening primrose oil (EPO) supplementation on vasodilatory prostacyclin (PGI2) and vasoconstrictory thromboxane A2 (TXA2) in 18 pre-eclamptic women between 31 and 36 weeks of gestation\textsuperscript{19}. The authors did not report any adverse effects on the women, the pregnancy outcome and any malformations in the newborns\textsuperscript{19}. Another study conducted on prostaglandin pathways in pre-eclamptic women did not report any risk in pregnancy associated with EPO\textsuperscript{20}.

A placebo controlled, partially double-blinded, clinical trial on the effects of evening primrose oil and fish oil in preventing pre-eclampsia of pregnancy did not report any adverse effects on the women or on the pregnancy outcomes, nor any malformations in the newborns\textsuperscript{10}.

A comparative study on the vascular sensitivity to angiotensin II in the mid-trimester of pregnancy in women after taking EPO did not report any adverse effects on the women or on the pregnancy outcomes, nor any malformations in the newborns\textsuperscript{11}. A comparative study on EPO and co-factors for prostaglandin synthesis in 10 pregnant and 10 non-pregnant women did not report any adverse effects on the women or on the pregnancy outcomes, nor any malformations in the newborns\textsuperscript{12}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratogenic and induces labour\textsuperscript{21}</td>
</tr>
</tbody>
</table>

A review of randomized double blind studies reported that gamma linolenic acid (GLA) increases prostaglandin E levels\textsuperscript{21}. It was recommended that GLA be avoided in pregnancy given the teratogenic and labor inducing effects of prostaglandin E agonists\textsuperscript{21}.  


EPO is widely used by many midwives to hasten cervical ripening in order to shorten labour and to decrease the incidence of postdate pregnancies. A survey of midwife in the United States found that 60% of midwives use EPO to induce labour. A two group retrospective quasi-experimental design on a sample of women, where they compared selected outcomes of 54 women taking evening primrose oil in their pregnancy with a control group of 54 women who did not showed that the oral administration of evening primrose oil from the 37th gestational week until birth did not shorten gestation or decrease the overall length of labour.

A two group retrospective quasi-experimental design reported that orally administered EPO may be associated with an increase in the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent and vacuum extraction.

**LACTATION**

A randomized controlled trial on the total fat and essential fatty acid contents of breast milk following EPO and placebo supplementation in 39 women for a period of 8 months starting between the 2nd and 6th months of lactation reported an increase in fatty acids in breast milk, but did not report any adverse effect to the infants or the mothers.
A study was conducted on whether formulae with EPO and fish oils raise long chain polyunsaturated fatty acids in plasma cholesterol esters, erythrocytes (RBC) and platelets (PLT) to levels encountered in breast-fed infants\textsuperscript{25}. The authors did not report any adverse effect to the infants\textsuperscript{25}.

**CONSTITUENTS\textsuperscript{26,27}**

2-16\% gamma-linolenic acid (GLA)

65-80\% linoleic acid

Vitamin E

**PHarmacology**

EPO has anti-inflammatory activity where EPO blocks the transformation of arachidonic acid to leukotrienes, increases the production of 1-series prostaglandins (PGE(1)), and acts as a competitive inhibitor of 2-series prostaglandins (PGE(2)) and 4-series leukotrienes\textsuperscript{26}.

EPO may help women with premenstrual syndrome (PMS) who have lower levels of GLA, possibly due to a defect in the conversion of linoleic acid to GLA\textsuperscript{28}.

EPO may help children with attention deficit-hyperactivity disorder (ADHD) who have lower levels of GLA\textsuperscript{29}.

EPO may lower plasma lipids and inhibit platelet aggregation\textsuperscript{30}.

EPO may improve neuronal blood supply and possibly prevent diabetic neuropathy\textsuperscript{31}.

EPO was found to reverse epidermal hyperproliferation in guinea pigs\textsuperscript{32}.

**DruG iNTeractions**

Anaesthesia\textsuperscript{33}

Anti-convulsant/Anti-seizure Drugs\textsuperscript{34}

Anticoagulant/Antiplatelet Drugs\textsuperscript{30}
Phenothiazines

PART USED

Seed

References


FALSE UNICORN

*Chamaelirium luteum*

**Synonyms/Common Names/Related Substances**

Blazing Star, fairywand, helonias, starwort

**INDICATIONS**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual complaints&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diuretic&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induces labour&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

False unicorn is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to false unicorn, mother’s cordial contains: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), blue cohosh (*Caulophyllum thalictroides*) and black cohosh (*Cimicifuga racemosa*).  

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine stimulant&lt;sup&gt;2, 3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emmenagogue&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A compendium for medicinal plants reported that false unicorn may have a uterine stimulant effect<sup>2, 3</sup>. A herbal contraindication and drug interaction compendium reported that false unicorn was an emmenagogue and contraindicated during pregnancy<sup>5</sup>. False unicorn was not reported in
the evidence-based medicine literature as having a uterine stimulant effect or being an
emmenagogue, nor was it reported as being contraindicated or safe in pregnancy.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigonadotrophic activity(^6)</td>
</tr>
<tr>
<td>Estrogenic(^7)</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that false unicorn had antigonadotrophic activity in rats and has estrogenic activity\(^6,7\).

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence based medicine literature of false unicorn being either safe or contraindicated during lactation.

**CONSTITUENTS**

No available information

**PHARMACOLOGY**

False unicorn is reported to have anthelmintic, diuretic, uterine stimulant and menstruation stimulant activity\(^3,8\).

**PARTS USED\(^1\)**

Root and rhizome

**References**


**FENNEL**

*Foeniculum vulgare*

**SYNONYMS/COMMON NAMES/RELATED COMPOUNDS**¹

Bitter fennel, carosella, common fennel, finnochio, Florence fennel, garden fennel, large fennel, phytoestrogen, sweet fennel, wild fennel

**INDICATIONS**

*Oil*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant colic²</td>
<td>B1</td>
</tr>
<tr>
<td>Chronic colitis (with <em>Taraxacum officinale, Hypericum perforatum, Calendula officinalis</em> and <em>Melissa officinalis</em>)³</td>
<td>C</td>
</tr>
<tr>
<td>Digestive complaints⁴</td>
<td>F</td>
</tr>
</tbody>
</table>

**PREGNANCY**

*Oil*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases uterine contractions⁵</td>
<td>3</td>
</tr>
</tbody>
</table>

A study on the effects of fennel essential oil on the rat uterus reported that fennel essential oil significantly reduced the intensity of oxytocin and PGE(2) induced contractions in the rat uterus and reduced the frequency of contractions induced by PGE(2)⁵.
A review article on the potential value of plants as sources of anti-fertility agents reported that fennel was a potential abortifacient and an emmenagogue.

A herbal toxicology and drug interaction compendium reported that fennel may have hormonal effects.

### Seed

| Level
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient</td>
</tr>
<tr>
<td>Emmenagoge</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that fennel seeds are an emmenagogue and have estrogenic activity.

### Food Amounts

| Level
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely safe</td>
</tr>
</tbody>
</table>

A natural product database reported that fennel is likely safe when consumed in food amounts.
**LACTATION**

| Level | Avoid\(^7\) | 4 |

A toxicology and drug interaction compendium reported that fennel oil should be avoided while breastfeeding\(^7\). There are no reports in the evidence-based literature of fennel oil being either safe or contraindicated during lactation.

**CAUTIONS**

Avoid long term use as estragole is a procarcinogen\(^9\).

Avoid oral use in liver disease or alcoholism, and during use of acetaminophen\(^7\).

Infants or toddlers\(^4,5\)

**CONSTITUENTS**

**Seed\(^{10,11}\)**

Beta-carotene

Vitamin C

Calcium

Magnesium

Iron

**Oil\(^1,7\)**

Anethole

Fenchone

Estragole
TOXICITY

Oil

Oral LD$_{50}$: 1.3g/kg to 4.5g/kg$^{5,7,12}$

Anethole

Oral LD$_{50}$: 2.09g/kg$^{13}$

PHARMACOLOGY

Anethole has estrogenic activity and may deplete liver glutathione$^{7,14}$.

Anethole and fenchone reduce upper respiratory tract secretions$^{14}$.

Anethole may be insecticidal and toxic$^{1}$

Aqueous fennel extract might increase mucociliary activity$^{14}$.

Fennel seed can promote GI motility, and in higher concentrations, can act as an antispasmodic$^{4}$.

Fennel may be allergenic$^{15}$.

Estragole is a procarcinogen that is not directly hepatotoxic or hepatocarcinogenic as it requires activation by liver enzymes to reach full toxicity$^{9}$.

DRUG INTERACTIONS

Ciprofloxacin (Cipro)$^{11}$

PART USED$^{1}$

Seed, oil

REFERENCES


FENUGREEK

*Trigonella foenum-graecum, Trigonella foenugraecum*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS\(^1\)

Alholva, bird's foot, bockshornklee, bockshornsame, foenugraeci semen, foenugreek, Greek clover, Greek hay, Greek hay seed, hu lu ba, methi, trigonella

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes(^2,5)</td>
<td>B2</td>
</tr>
<tr>
<td>Type 1 Diabetes(^6)</td>
<td>B2</td>
</tr>
<tr>
<td>Hyperlipidemia(^2,6,7)</td>
<td>B2</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudo-maple syrup urine disease(^8,9)</td>
<td>2</td>
</tr>
</tbody>
</table>

There are case reports of neonates being born with a peculiar odour following maternal consumption of fenugreek just before delivery\(^8,9\). In one study, the authors reported that the odour should not be confused with maple syrup urine disease and that there were no long term effects\(^8\). The odour is believed to originate from the fenugreek constituent sotolone\(^9\).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient(^10,11)</td>
<td>3</td>
</tr>
<tr>
<td>Uterine stimulant(^10,11)</td>
<td>3</td>
</tr>
<tr>
<td>Emmenagogue(^11)</td>
<td>4</td>
</tr>
</tbody>
</table>
Fenugreek extracts, both aqueous and alcoholic, have been shown to have a stimulating effect on the guinea pig uterus, especially during late pregnancy\(^\text{10}\). A review article on the potential value of plants as sources of anti-fertility agents reported that fenugreek is a potential abortifacient, emmanogogue and uterine stimulant\(^\text{11}\).

**Food**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^\text{11})</td>
<td>4</td>
</tr>
</tbody>
</table>

Fenugreek is reported to have minimal risk when taken in food amounts during pregnancy\(^\text{11}\).

**LACTATION**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactogogue(^\text{12,13})</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on fenugreek reports that there is anecdotal evidence that it stimulations lactation\(^\text{13}\). A clinical trial compared fenugreek versus torbangun, an plant used traditionally in Indonesia for lactation, and reported that fenugreek is frequently used by women to promote lactation\(^\text{13}\).

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential oxytocic activity(^\text{14})</td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal medicine compendium reported that fenugreek has potential oxytocic activity\(^\text{14}\).

**CAUTION**

Do not take with drugs as the mucilage content may decrease or delay drug absorption\(^\text{14}\)

**CONSTITUENTS**

Trigonelline\(^\text{14}\)

4-hydroxyisoleucine\(^\text{14}\)
Fenugreekine\textsuperscript{14}

**TOXICITY**

Oral LD\textsubscript{50}: 10g/kg\textsuperscript{15}

Acute oral LD\textsubscript{50}: >5g/kg\textsuperscript{16}

Intra-peritoneal LD\textsubscript{50}: 1.9g/kg\textsuperscript{15}

Acute dermal LD\textsubscript{50}: >2g/kg\textsuperscript{16}

**PHARMACOLOGY**

Fenugreek slows glucose absorption in the gastrointestinal tract\textsuperscript{17}.

Fenugreek and its constituent trigonelline have hypoglycemic activity\textsuperscript{14}.

The constituent 4-hydroxyisoleucine may directly stimulate insulin\textsuperscript{17}.

In patient with type 2 diabetes, fenugreek has been shown to increase beta-cell secretion, improve insulin resistance, significantly decrease triglyceride levels and increase in high-density lipoproteins\textsuperscript{2}.

Fenugreek seed consumption may decrease calcium oxalate deposition in the kidneys\textsuperscript{18}.

The constituent fenugreekine may have cardiotonic, hypoglycemic, diuretic, anti-inflammatory, antihypertensive, and antiviral properties\textsuperscript{14}.

**DRUG INTERACTIONS\textsuperscript{1}\textsuperscript{14}**

Diabetic drugs\textsuperscript{5,19}

Corticosteroids\textsuperscript{14}

Hormone therapy\textsuperscript{14}

Monoamine oxidase inhibitors (MAOIs)\textsuperscript{14}
PARTS USED

Seeds

REFERENCES


FEVERFEW

*Tanacetum parthenium*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Altamisa, bachelor's buttons, featherfoiul, featherfew, featherfoil, fever few, flirtwort midsummer daisy, santa maria, *Tanaceti parthenii*

INDICATIONS

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine headaches(^2,^3)</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue(^4)</td>
</tr>
<tr>
<td>Safety unknown</td>
</tr>
</tbody>
</table>

A herbal medicine compendium reported that feverfew is an emmenagogue\(^4\). There are no reports in the evidence-based medicine literature of feverfew being either safe or contraindicated during pregnancy.

LACTATION

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based medicine literature of feverfew being either safe or contraindicated during lactation.
CONSTITUENTS

Sesquiterpene lactone\textsuperscript{5}: parthenolide

Flavonoid glycoside\textsuperscript{6,7}: tanetin, apigenin, luteolin 7-glucuronides, quercetagetin, 6-hydroxykaempferol

Oil\textsuperscript{8}: chrysanthenyl acetate

Monoterpenes\textsuperscript{5}

Tannins\textsuperscript{5}

Melatonin\textsuperscript{9}

TOXICITY

A LD\textsubscript{50} value has not been estimated for feverfew\textsuperscript{4}.

Detailed blood analysis of 60 feverfew users (some > 1 year) did not show any significant differences when compared to that of controls\textsuperscript{10}.

Rats and guinea pigs fed feverfew (> 100 times the human daily dose for 5 weeks, and >150 times the human daily dose for 7 weeks; respectively) were identical to control animals, especially in regard to appetite and weight gain, and no adverse effects were reported\textsuperscript{11}.

Parthenolide at concentrations up to 800 mmol was found to be non-mutagenic\textsuperscript{12}.

Sesquiterpene lactones that contain an alpha-methylene butyrolactone ring are known to cause allergic reaction\textsuperscript{13,14}. Compounds with this structure are present in feverfew and reports of contact dermatitis have been documented\textsuperscript{15-18}.

PHARMACOLOGY

The constituent parthenolide was widely believed to be the active constituent in feverfew\textsuperscript{19,20}. It is now believed that other constituents are necessary in the prevention and treatment of migraines\textsuperscript{8,20-22}. 
Feverfew may inhibit platelet aggregation and inhibit serotonin release from platelets and leucocytes\textsuperscript{20, 23-27}.

Feverfew appears to block prostaglandin synthesis by inhibiting phospholipase, thereby preventing the release of arachidonic acid\textsuperscript{25, 28, 29}.

Feverfew may inhibit inflammation and pain transmission, and have an analgesic effect\textsuperscript{6, 30-32}.

Feverfew leaves and parthenolide may cause irreversible inhibition of vascular muscle contraction\textsuperscript{33, 34}.

The melatonin in feverfew may contribute to its pharmacological effect where migraines have been associated with decreased melatonin secretion\textsuperscript{9, 35}. Fresh or dried leaves contain significantly more melatonin than commercially prepared standardized feverfew tablets\textsuperscript{9}.

Feverfew has a cytostatic effect on tumor cell growth\textsuperscript{36}.

**DRUG INTERACTIONS\textsuperscript{1}**

Anticoagulant/antiplatelet drugs\textsuperscript{20, 23-27, 37}

Nonsteroidal anti-inflammatory drugs (NSAIDs)\textsuperscript{38, 39}

**PARTS USED**

Leaf\textsuperscript{4}

**REFERENCES**


FLAX

*Linum usitatissimum*

**SYNONYMS COMMON NAMES RELATED COMPOUNDS**

Flax seed, graine de lin, leinsamen, lini semen, linseed, lint bells, linum, phytoestrogen, winterlien

**INDICATIONS**

**Flaxseed**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Breast cancer prevention&lt;sup&gt;4-10&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Constipation&lt;sup&gt;11&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Menopausal symptoms&lt;sup&gt;12&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;12-14&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;15,16&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Coronary artery disease/ Atherosclerosis&lt;sup&gt;17&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Cystic mastalgia&lt;sup&gt;10,18&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Lupus nephritis&lt;sup&gt;19,20&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>HIV/AIDS (with arginine and yeast RNA)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Prostate cancer&lt;sup&gt;22&lt;/sup&gt;</td>
<td>D</td>
</tr>
</tbody>
</table>
### Oil

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia $^{15}$</td>
<td>B1</td>
</tr>
<tr>
<td>Hypertension $^{15,16}$</td>
<td>B2</td>
</tr>
<tr>
<td>Coronary artery disease/Atherosclerosis $^{17,23}$</td>
<td>C</td>
</tr>
<tr>
<td>Diabetes $^{14}$</td>
<td>C</td>
</tr>
</tbody>
</table>

#### PREGNANCY

**Flaxseed**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogenic/Anti-estrogenic effects $^{24-27}$</td>
<td>3</td>
</tr>
<tr>
<td>Lowers birth weight $^{24}$</td>
<td>3</td>
</tr>
</tbody>
</table>

Flaxseeds consumed during pregnancy were shown to have estrogenic and anti-estrogenic effects on newborn rats $^{24}$. Flaxseed had no effect on pregnancy outcome except that a 10% flaxseed diet lowered birth weight $^{24}$. A review article on the potential value of plants as sources of anti-fertility agents reported that flax has estrogenic activity $^{27}$.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not affect fetal development $^{25}$</td>
<td>3</td>
</tr>
<tr>
<td>Does affect fetal development $^{24,25}$</td>
<td>3</td>
</tr>
<tr>
<td>May alter reproduction $^{26}$</td>
<td>3</td>
</tr>
<tr>
<td>May affect estrous cycle $^{25}$</td>
<td>3</td>
</tr>
</tbody>
</table>
Female rat offspring from mothers fed flaxseed during pregnancy had shortened anogenital distance, greater uterine and ovarian relative weights, earlier age and lighter body weight at puberty, lengthened estrous cycle and persistent estrus\(^{24}\). The male rat offspring from mothers fed flaxseed during pregnancy had reduced postnatal weight gain and had greater sex gland and prostate relative weights\(^{24}\). Another study reported that flaxseed can potentially alter reproduction, depending on the dose and timing of exposure\(^{26}\).

Another study, however, reported that flaxseed ingestion during pregnancy did not affect fetal development but did affect indices of postnatal development such as the estrous cycle\(^{25}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases essential fatty acids in offspring serum and tissue(^{28})</td>
</tr>
</tbody>
</table>

Flaxseed increased alpha-linolenic (ALA) and eicosapentaenoic acid (EPA) and decreased arachidonic acid in serum and tissues of rat dams and offspring\(^{28}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not embyotoxic(^{29})</td>
</tr>
</tbody>
</table>

A study on the effect of flaxseed on rat embryos concluded that diets high in flaxseed or flaxseed meal do not result in serum factors that are directly embroyotoxic to organogenesis-staged rat embryos\(^{29}\).

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Strengthens bones prior to adulthood(^{30})</td>
</tr>
</tbody>
</table>

Female rat bone is more sensitive to the estrogen-like action of flaxseed lignans during early life when endogenous levels of sex hormones are low\(^{30}\). By adulthood, however, the improved bone strength does not persist\(^{30}\). Exposure to purified lignan does not have negative effects on bone strength\(^{30}\).
Quantitative information was collected on male reproductive effects in the rat of maternal and postnatal dietary exposure to flaxseed. It was reported that exposure to flaxseed does not adversely affect testis structure or spermatogenesis. A similar study also found that spermatogenesis was unaffected by flaxseed consumption.

A review article on the potential value of plants as sources of anti-fertility agents reported that flax was a potential abortifacient and an emmenagogue.

**Oil**

There are no reports in the evidence-based literature of flax oil being either safe or contraindicated during pregnancy.

**Food Amounts**

A natural product compendium reported that flaxseed and flax oil pose minimal risk during pregnancy if taken in food amounts.
LACTATION

Flaxseed

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A study on the effect of flaxseed supplementation during pregnancy and lactation reported that there were no significant effects of exposing male or female offspring to flaxseed during lactation<sup>30</sup>. They reported that their findings are in contrast to the estrogenic effects observed in male and female offspring exposed to flaxseed during fetal life and suggest that fetal life is a more hormone-sensitive period of development<sup>30</sup>. Although maternal feeding of flaxseed during lactation appears to be safe with respect to reproductive indices among offspring, the authors reported that future investigation is required to elucidate whether there are any long-term implications with respect to fertility<sup>30</sup>.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Estrogenic/Anti-estrogenic effects&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Flaxseeds consumed during pregnancy have estrogenic and anti-estrogenic effects on newborn rats<sup>24</sup>. As such, flaxseed was not recommended during lactation as its hormonal effect may impact of the developing infant<sup>24</sup>.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses into breast milk&lt;sup&gt;24, 34&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Through radioactive labeling, a study reported that flax lignans were transferred to the offspring via rat dam's milk<sup>24</sup>. Another study found that nervonic acid, found in flaxseed, is not readily transferred across the placental barrier but does readily cross the mammary epithelium and is incorporated into milk<sup>34</sup>. 
Flaxseed in the diet of lactating cows increased the beneficial fatty acids in milk without depressing nutrient digestibility\textsuperscript{35}. Flaxseed fed to cows increased milk protein percentage and its omega-6-to-omega-3-fatty-acids ratio\textsuperscript{36}.

### Oil

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based literature of flax oil being either safe or contraindicated during lactation.

### Food Amounts

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{1}</td>
</tr>
</tbody>
</table>

A natural product compendium reported that flaxseed and flax oil pose minimal risk during lactation if taken in food amounts\textsuperscript{1}.

### CONTRAINDICATIONS

Intestinal obstruction\textsuperscript{38}
Esophageal or gastrointestinal stricture

Acute gastroenteritis

Esophagitis

**CAUTION**

Large quantities of flaxseed can lead to intestinal obstruction if not taken with sufficient fluid.

**CONSTITUENTS**

**Seed**

Alpha-linolenic acid (ALA)

Cyanogenic glycosides (linamarin, linustatin, neolinustatin)

Lignan (secoisolariciresinol diglycoside)

Glutamic acid derivative (linatine)

Unsaturated fatty acids (linolenic acid, linoleic acid, oleic acid)

Soluble fiber mucilage (d-Xylose, L-Galactose, L-Rhamnose, d-Galacturonic acid)

Monoglycerides

Triglycerides

Sterols

Phenylpropane derivatives

**Oil**

Alpha-linolenic acid (ALA)

Unsaturated fatty acids (linolenic acid, linoleic acid, oleic acid)
TOXICITY

LD$_{50}$ of linatine: 2 mg (intraperitoneal)$^{38}$

PHARMACOLOGY

Flaxseed

Flaxseed is a bulk-forming fiber that stimulates intestinal peristalsis, thereby producing a laxative effect$^{41}$.

Flaxseed supplementation significantly increases n-3 polyunsaturated fatty acids in plasma and erythrocytes$^{13,42}$.

Since flaxseed reduces platelet aggregation and serum cholesterol, flaxseed thereby reduces the risk of atherosclerosis$^{43-47}$.

Flaxseed may have hypoglycemic activity and lower insulin levels in postmenopausal women$^{12,13}$.

Flaxseed is an abundant indirect food source of lignans, where lignans may have estrogenic and anti-estrogenic effects$^{48,49}$.

The lignans in flaxseed inhibit the growth of hormone-dependent breast cancer cells, inhibit mammary tumor growth in vitro, decrease cellular proliferation in mammary glands, increase mammary gland differentiation and reduce endogenous estrogen binding to estrogen receptors in breast cancer cells$^{40,48,50-59}$.

Alpha-linolenic acid was shown to reduce the growth of established tumors and have an anti-inflammatory effect$^{45,60}$.

The enzyme linamarase releases cyanide from linamarin, but linamarase is deactivated in normal gastric acid$^{38}$.

Grinding the seeds into a fine powder makes the cyanogenic glycosides more liable to hydrolysis and enhances the absorption of cyanide$^{38}$.
Oil

Flaxseed oil is among the best sources of alpha-linolenic acid\textsuperscript{43}.

Alpha-linolenic acid raises serum omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)\textsuperscript{42, 61}.

Flaxseed oil may lower triglyceride levels, increase systemic arterial elasticity and protect against ischemic stroke and lacunar infarction\textsuperscript{62-64}.

Flaxseed oil may decrease platelet aggregation\textsuperscript{45, 61}.

**DRUG INTERACTIONS\textsuperscript{1}**

Anticoagulant/antiplatelet drugs\textsuperscript{65}

Antidiabetes drugs\textsuperscript{12, 13}

Oral drugs\textsuperscript{66}

**PARTS USED\textsuperscript{1}**

Seed and oil

**REFERENCES**


30. Ward WE, Chen J, Thompson LU. Exposure to flaxseed or its purified lignan during suckling only or continuously does not alter reproductive indices in male and female offspring. J Toxcol Environ Health A 2001; 64:567-77.


**FOXGLOVE**

*Digitalis lanata, Digitalis purpurea*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**\(^1\)

Dead man's bells, fairy cap, fairy finger, foxglove, lady's thimble, lion's mouth, purple foxglove, Scotch mercury, throatwort, witch's bells, wolly foxglove

**INDICATIONS**

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure(^2)</td>
<td>A</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal malformations(^3)</td>
<td>1b</td>
</tr>
</tbody>
</table>

A serial examination of 20,248 livebirths, stillbirths and abortions in order to assess correlations between drug exposure and major malformations found a statistically significant association between digitalis and anomalies of the musculoskeletal system\(^3\).

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hydrops fetalis(^4-6)</td>
<td>2</td>
</tr>
</tbody>
</table>

There are a few cases in the evidence-based literature of digitalis being used to treat hydrops fetalis\(^4-6\). The treatment outcomes were successful in some cases and unsuccessful in others\(^4-6\).

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of fetal cardiac disorders(^7-10)</td>
<td>2</td>
</tr>
</tbody>
</table>
There are cases in the evidence-based literature where digitalis was used to treat fetal cardiac disorders, such as fetal tachycardia and fetal atrial flutter\textsuperscript{7-10}. The treatment outcomes were successful in some cases and unsuccessful in others\textsuperscript{7-10}.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be prescribed during pregnancy\textsuperscript{11,12}</td>
</tr>
<tr>
<td>4</td>
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</tbody>
</table>

Two review articles report that digitalis drug preparations can be prescribed during pregnancy\textsuperscript{11,12}.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic\textsuperscript{13}</td>
</tr>
<tr>
<td>4</td>
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</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that foxglove has cytotoxic activity\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Unsafe\textsuperscript{14}</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

A botanical safety compendium reports that digitalis is unsafe during pregnancy\textsuperscript{14}.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses the placenta\textsuperscript{15}</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

A review article in the evidence-based literature reported that digoxin rapidly crosses the placenta and reaches equilibrium with maternal and fetal serum having equal concentrations\textsuperscript{15}.

**LACTATION**

<table>
<thead>
<tr>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Unsafe\textsuperscript{14}</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
A botanical safety compendium reports that digitalis is unsafe during lactation\textsuperscript{14}. There are no reports in the evidence-based literature of digitalis being either safe or contraindicated during lactation.

**CONTRAINDICATIONS**

Second or third degree atrioventricular blocks\textsuperscript{16}

Hypercalcemia\textsuperscript{16}

Hypertrophic cardiomyopathy\textsuperscript{16}

Carotid sinus syndrome\textsuperscript{16}

Ventricular tachycardia\textsuperscript{16}

Thoracic aortic aneurysm\textsuperscript{16}

Wolff-Parkinson-White syndrome\textsuperscript{16}

**TOXICITY**

Toxic dose: 520 mg of powder\textsuperscript{16}

Lethal dose: 2 grams of powder\textsuperscript{16}

**CONSTITUENTS**

Cardiac (steroidal) glycosides\textsuperscript{16}: digitoxin (glycoside A), gitoxin (glycoside B), gitaloxin, digitonin \textit{(D. purpurea)}, digoxin, digitalin, gitaloxin, lanatosides A, B, C, D and E \textit{(D. lanata)}

Cardelonides\textsuperscript{16}

**PHARMACOLOGY**

Cardiac glycosides in digitalis increase cardiac contractility, decrease heart rate and reduce AV node conduction\textsuperscript{17}.

Digitalis increases cardiac output\textsuperscript{17}.
Digitalis relieves pulmonary congestion and peripheral edema\(^1\).

**DRUG INTERACTIONS**

Digoxin (Lanoxin)\(^1\)

Potassium depleting diuretics, Quinine\(^1,2\)

Stimulant laxatives\(^1,2\)

Tetracyclines and macrolide antibiotics (erythromycin-like drugs)\(^2\).

**PARTS USED**

Leaves, seeds, flowers\(^1\)

**REFERENCES**


GARLIC

*Allium sativum*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Aged garlic extract, ail, ajo, allii aativi bulbus, allium, camphor of the poor, clove garlic, garlic clove, nectar of the gods, poor man's treacle, rust treacle, stinking rose

INDICATIONS

**Garlic**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Hypercholesterolemia (mild effect)*2-14</td>
<td>A</td>
</tr>
<tr>
<td>Mild hypertension3, 12, 13, 15-17</td>
<td>A</td>
</tr>
<tr>
<td>Cancer prevention - stomach and colorectal18-21</td>
<td>A</td>
</tr>
<tr>
<td>Hypertriglyceridemia7-9, 11, 13</td>
<td>B1</td>
</tr>
<tr>
<td>Atherosclerosis3, 16, 22-24</td>
<td>B1</td>
</tr>
<tr>
<td>Anti-platelet aggregation16, 23, 25</td>
<td>B1</td>
</tr>
<tr>
<td>Unstable angina pectoris26</td>
<td>B2</td>
</tr>
<tr>
<td>Coronary artery disease11, 22</td>
<td>B2</td>
</tr>
<tr>
<td>Diabetes16, 27</td>
<td>B2</td>
</tr>
<tr>
<td>Tick repellant28</td>
<td>B2</td>
</tr>
<tr>
<td>Upper respiratory tract infection29</td>
<td>B2</td>
</tr>
<tr>
<td>Condition</td>
<td>Grade</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Acute otitis media (with <em>Verbascum thapsus</em>, <em>Calendula flores</em> and <em>Hypericum perforatum</em>)</td>
<td>B2</td>
</tr>
<tr>
<td>Cancer prevention – thyroid, breast, endometrial</td>
<td>C</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>C</td>
</tr>
<tr>
<td>Anti-fungal</td>
<td>C</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>D</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td>E</td>
</tr>
<tr>
<td>Anti - <em>Helicobacter pylori</em></td>
<td>E</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>E</td>
</tr>
</tbody>
</table>

*A systematic review of garlic powder in the treatment of moderate hyperlipidemia and concluded that garlic powder preparations significantly lowered serum triglyceride and total cholesterol compared to placebo*[^4]. A meta-analysis, however, concluded that garlic reduced total cholesterol by 0.65 mmol/L and was less effective in reducing total cholesterol than suggested by previous meta-analyses[^47].

**Aged Garlic extract**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia[^48]</td>
<td>B1</td>
</tr>
<tr>
<td>Hypertension[^48]</td>
<td>B1</td>
</tr>
</tbody>
</table>

[^4]: [Reference](#)  
[^47]: [Reference](#)
## PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk – Third trimester&lt;sup&gt;49&lt;/sup&gt;</th>
<th>1a</th>
</tr>
</thead>
</table>

A randomized controlled study was conducted where 100 primigravidas were treated with either garlic tablets (800 mg/day) or placebo during the third trimester of pregnancy in order to determine the effect of garlic supplementation on preeclampsia<sup>49</sup>. With the exception of a garlic body odour, few side effects (e.g. feeling of nausea) were reported as a result of garlic supplementation during the third trimester of pregnancy<sup>49</sup>. Pregnancy outcomes were comparable in both the group treated with garlic and the placebo group<sup>49</sup>. The authors did not report any incidence of major or minor malformations in the newborn infants nor any spontaneous abortions of the fetus<sup>49</sup>.

<table>
<thead>
<tr>
<th>Level</th>
<th>Garlic crosses into the amniotic fluid&lt;sup&gt;50&lt;/sup&gt;</th>
<th>1a</th>
</tr>
</thead>
</table>

Amniotic fluid samples were obtained from 10 pregnant women undergoing routine amniocentesis procedure, where five of the women ingested placebo capsules while the remaining five ingested capsules containing the essential oil of garlic<sup>50</sup>. The odour of the amniotic fluid obtained from four of the five women who had ingested the garlic capsules was judged to be stronger or more like garlic than the samples collected from the women consuming placebo capsules<sup>50</sup>. Thus, it was concluded that garlic ingestion by pregnant women significantly altered the odor of their amniotic fluid<sup>50</sup>.

<table>
<thead>
<tr>
<th>Level</th>
<th>Potential abortifaciens&lt;sup&gt;51&lt;/sup&gt;</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emmenagogue&lt;sup&gt;51&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Uterine stimulant&lt;sup&gt;51&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>
A review article on the potential value of plants as sources of anti-fertility agents reported that garlic was a potential abortifacient, emmenagogue and uterine stimulant\textsuperscript{51}.

**LACTATION**

| Minimal risk\textsuperscript{52} | 1a |

In nursing infants, maternal garlic ingestion did not significantly affect the number of times the infants fed nor the amount of milk they consumed\textsuperscript{52}. Although benign, short-term behavioural changes were observed in the infants as nursing mothers went from placebo to garlic supplementation and vice versa\textsuperscript{52}. The authors did not report any adverse effects in the nursing infants nor in breast milk production by the mothers\textsuperscript{52}.

**CONSTITUENTS**

Sulphur-containing compounds\textsuperscript{9,53,54}: alliin, allicin (diallyl thiosulphinate), allyl propyl disulphide, diallyl disulphide, diallyl trisulphide, ajoene, vinylthiinies

S-allylmercaptocysteine (ASSC)\textsuperscript{54}

S-methylmercaptocysteine (MSSC)\textsuperscript{54}

Volatile oils\textsuperscript{54}

**PHARMACOLOGY**

Garlic has lipid-lowering effects through inhibition of the cholesterolgenic enzymes 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase and acetyl-CoA synthetase, through increased loss of bile salts in feces, and through mobilization of tissue lipids into circulation \textsuperscript{9,55-58}.

Garlic has anti-atherogenic action *in vitro and in vivo* where it inhibited the proliferative activity of atherosclerotic plaques in the human aorta, reduced cholesterol accumulation in blood serum, and made LDL significantly more resistant to oxidation than LDL isolated from subjects receiving no garlic supplements\textsuperscript{59,60}. 
Garlic inhibits platelet aggregation in healthy individuals and patients with cardiovascular disease, and inhibits platelet adhesion to collagen, fibrinogen and von Willebrand factor\textsuperscript{22,61,62}.

Garlic increased fibrinolytic activity during long term use in chronic infarction cases as well as during the critical acute post-infarction period\textsuperscript{22}.

Garlic has anti-platelet activity\textsuperscript{9,16,23}

Garlic was found to reduce arterial blood pressure by causing membrane hyperpolarization and subsequent vasodilation through its action on K(Ca) ion channels in the membrane of vascular smooth muscle cells\textsuperscript{3}.

Garlic oil reduced blood sugar in men and increased blood sugar in women\textsuperscript{27}.

Garlic detoxifies chemical carcinogens, prevents carcinogenesis and directly inhibits the growth of cancer cells\textsuperscript{42}.

Garlic stimulates the immune system by stimulating macrophage activity, natural killer cells, and LAK cells, and by increasing the production of IL-2, TNF and interferon-gamma\textsuperscript{42}.

Garlic protects against the suppression of immunity by chemotherapy and ultraviolet radiation through the stimulation of macrophages and lymphocytes\textsuperscript{42}.

Garlic oil was found to reduce the activity of cytochrome P450 CYP2E1\textsuperscript{63}.

Garlic was shown to significantly increase maximum oxygen consumption (VO2max) and endurance performance time of endurance athletes\textsuperscript{64}.

Garlic, with \textit{Verbascum thapsus}, \textit{Calendula flores} and \textit{Hypericum perforatum}, was an effective anaesthetic during acute otitis media ear pain\textsuperscript{30}.

Garlic has \textit{in vitro} activity against \textit{Helicobacter pylori}\textsuperscript{44,45}.

Garlic has antimycotic, anti-fungal and antibacterial activity\textsuperscript{35-40,65}

\textbf{DRUG INTERACTIONS}

Anti-coagulant/anti-platelet drugs\textsuperscript{22,61}
Anti-glycemic drugs, Highly active anti-retroviral therapy (HAART) drugs, Oral contraceptives, Drugs metabolized by cytochrome P450 CYP2E1 enzyme

PARTS USED

Bulb

REFERENCES


GENTIAN

_Gentiana lutea_

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Bitter root, bitterwort, gall weed, gentiana, _Gentianae radix_, pale gentian, stemless gentian, yellow gentian, wild gentian

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic and acute sinusitis (with elderberry, vervain, primrose and sorrel)</td>
<td>B1</td>
</tr>
<tr>
<td>Digestive disorders, appetite disorders and constipation (with rhubarb, boldus and cascara)</td>
<td>B1</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Mutagen</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential mutagen</td>
<td>3</td>
</tr>
</tbody>
</table>

The gentian constituents gentisin and isogentisin were reported to have mutagenic effects on bacteria.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue</td>
<td>4</td>
</tr>
</tbody>
</table>

A herbal compendium reported that gentian is an emmenagogue. There are no reports in the evidence-based literature of gentian being either safe or contraindicated during pregnancy.
LACTATION

| Potential mutagen⁵,⁶ | 3 |

The gentian constituents gentisin and isogentisin were reported to have mutagenic effects on bacteria⁶.

| Unknown | 5 |

There are no reports in the evidence-based medicine literature of gentian being either safe or contraindicated during lactation.

CONTRAINDICATIONS

Acute gastrointestinal inflammation or irritation⁷

Peptic ulcer⁷

TOXICITY

100 g of gentian root was reported to yield approximately 100 mg of total mutagenic compounds, of which gentisin and isogentisin comprised 76%⁸.

CONSTITUENTS

Iridoid monoterpenes⁷: amarogentin, gentiopicrin, swertiamarin, sweroside

Hydroxyxanones⁸: gentisin, isogentisin

PHARMACOLOGY

The bitter constituents, gentiamarin, gentiopicrin, amarogentin and swertiamarin, appear to increase saliva and digestive secretion⁵,⁹.

Gentianine may have anti-inflammatory activity¹⁰.
Gentisin and isogentisin have been shown to be mutagenic in bacterial studies\(^5\).

Gentiopicrin is lethal to mosquito larvae\(^{10}\).

**DRUG INTERACTIONS\(^1,11\)**

Antacids\(^{11}\)

H-2 antagonists\(^{11}\)

Proton pump inhibitors\(^{11}\)

**PARTS USED**

Root\(^1\)

**REFERENCES**


# GINGER

*Zingiber officinalis*

**SYNONYMS/COMMON NAMES/RELATED COMPOUNDS**

African ginger, black ginger, cochin ginger, gingembre, ginger root, imber, Jamaica ginger, jiang, race ginger, shoga, *Zingiberis rhizome*

**INDICATIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting&lt;sup&gt;2&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Hyperemesis gravidarum - Nausea and vomiting of pregnancy&lt;sup&gt;3-9&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Hyperemesis gravidarum - Nausea and vomiting of pregnancy (with vitamin B6)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Post-operative nausea and vomiting&lt;sup&gt;10-12&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Chemotherapy induced nausea&lt;sup&gt;13,14&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Vomiting from motion sickness&lt;sup&gt;15,16&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Rheumatoid Arthritis&lt;sup&gt;17,18&lt;/sup&gt;</td>
<td>D</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk (up to 1,500 mg of dried ginger per day)&lt;sup&gt;3-9&lt;/sup&gt;</td>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial was conducted on 120 women (< 20 weeks pregnant) with symptoms of morning sickness<sup>4</sup>. Patients received a ginger extract, equivalent to 1,500 mg of...
dried ginger, for four days\textsuperscript{4}. After 4 days, there were significant improvements in nausea and retching\textsuperscript{4}. Post-delivery follow-ups revealed normal ranges of birth weight, gestational age and APGAR score\textsuperscript{4}. The frequency of congenital abnormalities in the ginger group infants was comparable to the general population of infants born at the time of this study\textsuperscript{4}.

Another randomized controlled trial was conducted on 70 pregnant women where they received 1,000 mg of dried ginger per day\textsuperscript{5}. Nausea and vomiting decreased significantly and no adverse effects on pregnancy or pregnancy outcomes were reported\textsuperscript{5}. Similar results were found 2 other studies were pregnant women took 1,000 mg per day\textsuperscript{6-9}.

Another randomized controlled trial was conducted on 138 pregnant women (< 16 weeks pregnant) where one group received 500 mg of ginger and the other received 10 mg of vitamin B6\textsuperscript{3}. In both groups, symptoms of nausea and vomiting were improved, and no adverse effects during pregnancy and post delivery were reported\textsuperscript{3}. A similar study was conducted on ginger and B6 with 291 pregnant women and reported the same results\textsuperscript{8}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely cause of spontaneous abortion\textsuperscript{6}</td>
</tr>
</tbody>
</table>

During a randomized double blind crossover trial, one woman in the study experienced a spontaneous abortion in her 12\textsuperscript{th} week of pregnancy\textsuperscript{6}. The authors reported that one spontaneous abortion in 27 pregnancies was not a suspicious high rate of fetal wastage in early pregnancy\textsuperscript{6}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not increase rates of major malformations\textsuperscript{7}</td>
</tr>
</tbody>
</table>

A prospective cohort study with matched controls was conducted on 187 pregnancies where the pregnant women had taken ginger during their pregnancy\textsuperscript{7}. The researchers concluded that ginger does not increase the rates of major malformations above the baseline rate of 1% to 3%\textsuperscript{7}. 

Ginger extracts when administered to pregnant rats during the period of organogenesis, caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight\textsuperscript{19}. The constituents 6-gingerol and shogaol have been shown to be mutagenic in bacterial cultures while zingerone has been shown to be anti-mutagenic and offset the mutagenic effects of 6-gingerol and shogaol\textsuperscript{20-22}. 

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Non-mutagenic, non-teratogenic\textsuperscript{19} | 3  
| Mutagenic constituents\textsuperscript{20,21} | 3  
| Anti-mutagenic constituents\textsuperscript{22} | 3  

A study on rats reported that in utero exposure to ginger tea resulted in increased early embryo loss and in increased growth in surviving fetuses\textsuperscript{23}. Embryonic loss in the ginger tea treatment groups was double that of the controls\textsuperscript{23}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Potential embryotoxicity\textsuperscript{23} | 3  

A review article on the treatments for nausea during pregnancy reported that the existing treatments, including ginger, showed no evidence of teratogenicity\textsuperscript{24}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Non-teratogenic\textsuperscript{24} | 4  

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Potential testosterone receptor blocker\textsuperscript{25} | 4  

Via inhibition of thromboxane synthetase, it has been proposed that ginger may affect testosterone receptor binding in the fetus, thereby potentially affecting sex steroid differentiation of the fetal brain$^{25}$. 

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsafe$^{26}$</td>
</tr>
</tbody>
</table>

A literature survey of 300 non-medical sources reported that 16 sources report ginger as unsafe during pregnancy$^{26}$. 

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient$^{27}$</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that ginger is a potential abortifacient$^{27}$. 

**Dose >1,000 mg daily** 

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue$^{28}$</td>
</tr>
<tr>
<td>Mutagenic$^{28}$</td>
</tr>
<tr>
<td>Anti-platelet$^{28}$</td>
</tr>
</tbody>
</table>

A botanical safety compendium reported that consuming more than 1,000 mg of ginger per day during pregnancy was not advised due to potential emmenagogue, mutagenic and anti-platelet effects$^{28}$. 

LACTATION

<table>
<thead>
<tr>
<th>Mutagenic constituents(^{20,21})</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-mutagenic constituents(^{22})</td>
<td>3</td>
</tr>
</tbody>
</table>

The constituents 6-gingerol and shogaol have been shown to be mutagenic while zingerone has been shown to be anti-mutagenic and offset the mutagenic effects of 6-gingerol and shogaol\(^{20-22}\).

| Unknown | 5 |

There are no reports in the evidence-based scientific literature of ginger being either safe or contraindicated during lactation.

CAUTION

Gallstones\(^{29}\)

Gastric ulcers

CONSTITUENTS

Non-volatile constituents\(^{30}\): 6-gingerol, (6)-shogaol, (6)- and (10)-dehydro-gingerdione, (6)- and (10)-gingerdione, zingerone

Oleoresins\(^{30}\)

Proteolytic enzyme\(^{30}\): zingibain (a)

TOXICITY

LD\(_{50}\) (intraperitoneal): 500mg/kg\(^{31}\)
No evidence of teratogenicity or mutagenicity at daily doses of up to 1000 mg/kg body weight in rats\textsuperscript{19}

**PHARMACOLOGY**

The constituent 6-gingerol is believed to be responsible for ginger’s anti-emetic activity\textsuperscript{32}.

Most of ginger’s anti-emetic activity is localized to the gastrointestinal tract tract\textsuperscript{32}.

The constituent galanolactone acts primarily on 5-HT3 receptors in the ileum, which are the same receptors affected by some prescription anti-emetics\textsuperscript{32}.

Ginger’s anti-emetic activity may also involve the central nervous system, where constituents 6-shogaol and galanolactone act on serotonin receptors\textsuperscript{32}.

Ginger does not affect GI emptying time\textsuperscript{33, 34}.

Ginger may inhibit cyclooxygenase (COX) and lipooxygenase pathways, thereby having anti-inflammatory activity\textsuperscript{18}.

Ginger may inhibit platelet thromboxane, thereby having anti-platelet activity\textsuperscript{35}.

The constituents 6-gingerol and shogaol have been shown to be mutagenic in bacterial cultures while zingerone has been shown to be anti-mutagenic and offset the mutagenic effects of 6-gingerol and shogaol\textsuperscript{20-22}.

A study on rats reported that *in utero* exposure to ginger tea resulted in increased early embryo loss and in increased growth in surviving fetuses\textsuperscript{23}.

Ginger may have hypoglycemic, hypotensive or hypertensive, hypocholesterolemic, anthelmintic and gastroprotective effects\textsuperscript{36}.

Via inhibition of thromboxane synthetase, it has been proposed that ginger may affect testosterone receptor binding in the fetus, thereby potentially affecting sex steroid differentiation of the fetal brain\textsuperscript{25}. 
DRUG INTERACTIONS

Acid-inhibiting drugs

Anticoagulant/antiplatelet drugs

Barbiturates

Blood pressure therapy

Cardiac drugs

Diabetic drugs

PARTS USED

Rhizome and root

REFERENCES


GINKGO

Ginkgo biloba

SYNONYMS COMMON NAMES RELATED SUBSTANCES

Adiantifolia, bai guo ye, fossil tree, Ginkgo folium, ginkgo leaf, ginkyo, Japanese silver apricot, kew tree, maidenhair tree, salisbury, Salisburia adiantifolia, yinhsing, baiguo

INDICATIONS

Leaf

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication – Peripheral vascular disease</td>
<td>A</td>
</tr>
<tr>
<td>Dementia (Alzheimer’s disease and other)</td>
<td>A</td>
</tr>
<tr>
<td>Cerebrovascular insufficiency</td>
<td>A</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>A</td>
</tr>
<tr>
<td>Age-associated memory impairment</td>
<td>B1</td>
</tr>
<tr>
<td>Memory enhancement in healthy individuals</td>
<td>B1</td>
</tr>
<tr>
<td>Altitude sickness</td>
<td>B1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>B1</td>
</tr>
<tr>
<td>Premenstrual syndrome (PMS)</td>
<td>B1</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>B2</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>C</td>
</tr>
<tr>
<td>Antidepressant-induced sexual dysfunction</td>
<td>C</td>
</tr>
</tbody>
</table>
### Seed

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>E</td>
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</tbody>
</table>

### Light-induced retinal damage

#### E

A case series in the literature reported the presence of colchicine in the placental blood of pregnant women having taken ginkgo. The source of colchicine was traced back to the consumption of commercially available ginkgo biloba products that contained colchicine. Given that colchicine is not a common constituent of ginkgo, the observed finding is most likely due to an adulteration of a ginkgo product by a herb containing colchicine.

### Leaf

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
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</tbody>
</table>

A case series in the literature reported the presence of colchicine in the placental blood of pregnant women having taken ginkgo. The source of colchicine was traced back to the consumption of commercially available ginkgo biloba products that contained colchicine. Given that colchicine is not a common constituent of ginkgo, the observed finding is most likely due to an adulteration of a ginkgo product by a herb containing colchicine.

### Antiplatelet

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>3</td>
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</table>

The antiplatelet properties of ginkgo leaf may prolong bleeding during delivery.
<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue&lt;sup&gt;34&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Hormonal changes&lt;sup&gt;34&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>

A herb toxicology and drug interaction compendium reported that ginkgo leaf is an emmenagogue and can cause hormonal changes<sup>34</sup>. Ginkgo leaf was not reported in the evidence-based medicine literature as being an emmenagogue or causing hormonal changes, nor was it reported as being contraindicated in pregnancy.

**Roasted seed**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly safe if taken as food&lt;sup&gt;35&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>

A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during pregnancy<sup>35</sup>. Roasted ginkgo seed was not reported in the evidence-based medicine literature as being either safe or contraindicated in pregnancy.

**Raw Seed**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly unsafe&lt;sup&gt;36&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>

A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in pregnancy if they are used medicinally<sup>36</sup>. Raw ginkgo seeds were not reported in the evidence-based medicine literature as being either safe or contraindicated in pregnancy.
LACTATION

Leaf

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Ginkgo leaf was not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

Roasted seed

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly safe if taken as food(^{35})</td>
</tr>
</tbody>
</table>

A toxicology compendium reported that roasted ginkgo seeds may be potentially safe if eaten as a food during lactation\(^{35}\). Roasted ginkgo seed was not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

Raw Seed

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly unsafe(^{36})</td>
</tr>
</tbody>
</table>

A toxicology compendium reported that raw ginkgo seeds (non-roasted) may be a concern in lactation if they are used medicinally\(^{36}\). Raw ginkgo seeds were not reported in the evidence-based medicine literature as being either safe or contraindicated in lactation.

CONSTITUENTS

Leaf

Flavonoids\(^{37}\): rutin, isorhamnetine, quercetin, kaempferol, proanthocyanidins

Terpenoids\(^{5}\): ginkgolides A, B, C, M and J, bilobalide
Organic acids

Seed

Cyanogenic glycosides

Ginkgotoxin

TOXICOLOGY

Leaf

LD$_{50}$ in mice: 7,725mg

Crude extracts of ginkgo leaf may contain ginkgolic acids, which are suspected to have cytotoxic, allergenic, mutagenic and carcinogenic properties.

Seed

Ginkgotoxin, found in ginkgo seed, may cause seizures, loss of consciousness and death.

PHARMACOLOGY

Leaf

Ginkgo increases cerebral and peripheral blood circulation.

Ginkgo reduces vascular permeability, causes vascular contraction, improves venous tone, inhibits phosphodiesterase type 4 (PDE4), relaxes vascular smooth muscle via a nitric oxide pathway and improves blood flow to the corpus cavernosum of the penis.

Ginkgo reduces platelet aggregation by competitively binding platelet activating factor (PAF) and by inhibiting the formation of platelet thromboxane A$_2$.

The ginkgo flavonoids have antioxidant and free radical scavenging properties.

Partially due to its antioxidant activity, ginkgo inhibits the toxicity and cell death induced by beta-amyloid plaques in Alzheimer’s disease.
Ginkgo decreases systolic and diastolic blood pressure, increases fasting plasma insulin and C-peptide, decreases cortisol secretion and decreases the secretion of corticotropic releasing hormone (CRH)\textsuperscript{32, 47, 48}.

Ginkgo may have cholinergic effects and may or may not have a monoamine oxidase inhibitor (MAOI) effect in the central nervous system\textsuperscript{7, 49-51}.

Ginkgo may reverse the decline in brain alpha-adrenoceptor activity that occurs with aging\textsuperscript{45}.

Ginkgo decreases phagocyte chemotaxis, decreases smooth muscle contraction, prevents degranulation of neutrophils, decreases free radical production, decreases damaging glycine production after brain injury and reduces excitatory amino acid receptor function\textsuperscript{5, 45, 52}.

Ginkgo may inhibit cytochrome P450 3A4, induce cytochrome P450 3A5 and mildly inhibit cytochrome P450 1A2 and 2D6\textsuperscript{1, 53, 54}.

\textit{Seed}

Cyanogenic glycosides may have antibacterial and antifungal effects\textsuperscript{1, 36}.

**DRUG INTERACTIONS**

\textit{Leaf}

Anticoagulant/Antiplatelet Drugs\textsuperscript{30, 32, 33}.

Fluoxetine\textsuperscript{55}.

Buspirone\textsuperscript{55}.

St. John’s wort\textsuperscript{55}.

Melatonin\textsuperscript{55}.

Insulin\textsuperscript{32}.

Monoamine oxidase inhibitors (MAOIs)\textsuperscript{49-51}.

Seizure threshold lowering drugs\textsuperscript{56, 57}.
Thiazide diuretics\textsuperscript{58}.

Trazodone\textsuperscript{54}.

Warfarin\textsuperscript{59}.

Drugs metabolized by cytochrome P4503A4, P450 3A5, P450 1A2 and P450 2D6 enzymes\textsuperscript{1,53,54}.

**PARTS USED**

Leaf, seed\textsuperscript{1}

**References**


GOLDENSEAL

*Hydrastis canadensis*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Eye balm, eye root, goldenroot, goldsiegel, ground raspberry, *Hydrastis*, Indian dye, Indian plant, Indian tumeric, jaundice root, orange root, sceau d'or, warnera, wild curcuma, yellow Indian paint, yellow paint, yellow puccoon, yellow root.

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine-resistant malaria (with pyrimethamine)</td>
<td>B1</td>
</tr>
<tr>
<td>Infectious diarrhea</td>
<td>B1</td>
</tr>
<tr>
<td>Trachoma (<em>Chlamydia trachomatis</em> eye infection)</td>
<td>B2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>C</td>
</tr>
<tr>
<td>Anti-<em>Helicobacter pylori</em></td>
<td>E</td>
</tr>
<tr>
<td>Antitubercular</td>
<td>E</td>
</tr>
<tr>
<td>Narcotic concealment</td>
<td>E</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>E</td>
</tr>
<tr>
<td>Cancer prevention</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause newborn jaundice (kernicterus)</td>
<td>3</td>
</tr>
</tbody>
</table>
In rats, berberine displaces bilirubin bound to albumin\textsuperscript{17}. Berberine (10-20ug/g) was administered intraperitoneally to adult rats on a daily basis for 1 week\textsuperscript{17}. After one week, a significant decrease in mean bilirubin serum protein binding was observed, due to an \textit{in vivo} displacement effect by berberine\textsuperscript{17}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{17}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Uterine stimulant\textsuperscript{18-20}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that goldenseal contains the uterine stimulant berberine\textsuperscript{18, 19}. A herbal and drug interaction compendium reported that goldenseal also contains the uterine stimulant components hydrastine, canadine and hydrastinine\textsuperscript{20}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocic effects\textsuperscript{18, 21}</td>
</tr>
</tbody>
</table>

Two herbal toxicology compendia reported that goldenseal has oxytocic effects during pregnancy\textsuperscript{18, 21}. Goldenseal, however, was not reported in the evidence-based medicine literature as having oxytocic properties.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause or aggravate newborn jaundice (kernicterus)\textsuperscript{17}</td>
</tr>
</tbody>
</table>

In rats, berberine displaces bilirubin bound to albumin\textsuperscript{17}. Berberine (10-20ug/g) was administered intraperitoneally to adult rats on a daily basis for 1 week\textsuperscript{17}. After one week, a significant decrease in mean bilirubin serum protein binding was observed, due to an \textit{in vivo} displacement effect by berberine\textsuperscript{17}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{17}. 


CONTRAINDICATION

Newborn jaundice (kernicterus)\(^{17}\)

CONSTITUENTS

Isoquinoline alkaloids\(^{8,20,22}\): hydrastine, berberine, tetrahydroberberastine, berberastine, canadalone, canadine, hydrastinine, beta-hydastine

TOXICOLOGY

LD\(_{50}\) of berberine in humans\(^{18}\): 27.5 mg/kg

PHARMACOLOGY

Berberine was found to displace bilirubin bound to albumin in vitro\(^ {17}\). Berberine was found to be about ten times superior to phenylbutazone, a known potent displacer of bilirubin, and about one hundred times superior to papaverine, a berberine-type alkaloid\(^ {17}\).

Hydrastine and berberine have been shown to have antibacterial activity\(^ {12,13,23-26}\).

Hydrastine and berberine have been shown to have amebicidal, anti-parasitic (trypanocidal) and anti-fungal activity\(^ {23,27-30}\).

Berberine and beta-hydastine were shown to have anti-*Helicobacter pylori* activity in vitro\(^ {8}\).

Berberine derived from goldenseal has been shown to have antitubercular activity in vitro\(^ {9}\).

At low doses hydrastine may have a hypotensive effect, while at higher doses, hydrastine constricts peripheral blood vessels and may potentially cause a hypertensive effect\(^ {21}\).

In low doses, berberine may act as a cardiac and respiratory stimulant, while in high doses it may act as a cardiac and respiratory depressant\(^ {18,23,31}\).

Berberine was shown to have anti-platelet activity\(^ {32}\).

Goldenseal was shown to increase immune function and berberine was shown to have anti-inflammatory effects\(^ {33-37}\).
Berberine was found to have an antidiarrheal effects\textsuperscript{38}.

Berberine was found to inhibit parathyroid hormone (PTH)-stimulated bone resorption, inhibit osteoclastic bone resorption and prevent a decrease in bone mineral density of the lumbar vertebra\textsuperscript{39}.

Goldenseal may interfere with cytochrome P450 3A4 (CYP3A4) enzyme\textsuperscript{40}.

**DRUG INTERACTIONS**

Acid-inhibiting drugs\textsuperscript{1,41}

Antihypertensive agents\textsuperscript{21}

Barbiturates\textsuperscript{21}

Anticoagulant drugs\textsuperscript{32}

Highly protein bound drugs\textsuperscript{17}

Sedative drugs\textsuperscript{21}

Drugs metabolized by cytochrome P450 3A4 (CYP3A4) enzyme\textsuperscript{40}

**PARTS USED\textsuperscript{20}**

Root, rhizome

**REFERENCES**


GREEN TEA

Camellia sinensis

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Camellia thea, Camellia theifera, Chinese tea, EGCG, Japanese tea, tea, tea green, Thea sinensis, Thea boeha, Thea viridis

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer prevention(^{2-8})</td>
<td>A</td>
</tr>
<tr>
<td>Oral leukoplakia(^{9})</td>
<td>B1</td>
</tr>
<tr>
<td>Improves cognitive performance(^{10})</td>
<td>C</td>
</tr>
<tr>
<td>Elevated cholesterol and triglycerides(^{11})</td>
<td>C</td>
</tr>
<tr>
<td>Cardiovascular disease prevention(^{11})</td>
<td>C</td>
</tr>
<tr>
<td>Liver disease prevention(^{11})</td>
<td>C</td>
</tr>
<tr>
<td>Parkinsonism prevention(^{12})</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Risk</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^{13})</td>
<td>1b</td>
</tr>
</tbody>
</table>

A comparison study on the effects of green tea consumption on iron absorption during pregnancy was conducted\(^{13}\). Pregnant women were given sodium ferrous citrate along with green tea in one group and water in another\(^{13}\). The authors reported that green tea did not interfere with iron absorption nor did they report any serious side effects in the pregnant women\(^{13}\).
### Spontaneous abortion

A case-control study of 3,149 pregnant women reported that serum paraxanthine concentration, a caffeine metabolite, was higher in women who had spontaneous abortions than in controls. A case-control study of 1,498 pregnant women reported that the consumption of 375 mg or more caffeine per day during pregnancy may increase the risk of spontaneous abortion.

### Increased risk of still birth

A prospective follow up study on 18,478 singleton pregnancies in women with valid information about coffee consumption during pregnancy reported that pregnant women who drink 8 or more cups of coffee per day have double the risk of stillbirth, when compared to women who do not drink coffee during pregnancy. Although this study was related to coffee, there could also be an increased risk of still birth with proportional intake of green tea.

### Low birth weight infants

A large prospective study on 2,291 mothers reported that women consuming more than 600 mg of caffeine per day are at greater risk for having low birth weight infants. A prospective study on 63 women reported that pregnant non-smokers consuming caffeine more than 300 mg/day had statistically significant lower weights of newborns and placentas (p < 0.05).

### Teratogenic compounds

Elevated caffeine intake causes histopathologically teratogenic effects on newborn rat cornea. A review study, however, reported that when caffeine is administered in fractioned quantities during the day, as it is the case with human caffeine intake, caffeine is no longer a teratogen in animals.
A compendium on the safety of drugs in pregnancy and lactation reported that over 3 cups of caffeine a day (300 mg) may be harmful to the fetus\textsuperscript{24}.

A drug compendium and a review study reported that approximately 300 mg of caffeine consumed throughout the day seems safe during pregnancy\textsuperscript{25, 26}.

**LACTATION**

Elevated caffeine intake causes histopathologically teratogenic effects on newborn rat cornea\textsuperscript{19}. Since caffeine appears in breast milk at half the concentration as in the mother’s plasma, newborns may be exposed to teratogenic compounds\textsuperscript{27}. A review study, however, reported that when caffeine is administered in fractioned quantities during the day, as it is the case with human caffeine intake, caffeine is no longer a teratogen in animals\textsuperscript{23}.

A compendium on herbal medicine reported that nursing mothers who consume caffeine may have infants with sleeping disorders\textsuperscript{28}.

**CONSTITUENTS**

Polyphenols\textsuperscript{29, 30}: gallic acid
Catechins\textsuperscript{29,30}: epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC)

Caffeine 2-4\% or 10-80 mg caffeine per cup\textsuperscript{31-33}.

**TOXICITY**

Caffeine doses greater than 1 \text{g/(body surface in meters)}^2 taken 3 times daily are associated with a higher incidence of side effects\textsuperscript{34}.

**PHARMACOLOGY**

ECG appears to induce apoptosis in cancer cells by reactive oxygen species formation and mitochondrial depolarization\textsuperscript{30}.

EGCG may have anti-angiogenic activity by preventing new blood vessel growth in tumors and may inhibit tumor cell proliferation\textsuperscript{34-37}.

The catechins may reduce lipoprotein oxidation and proliferation of vascular smooth muscle that occurs with high concentrations of low-density lipoproteins\textsuperscript{38-41}.

Topically, EGCG and epicatechin-3-gallate may protect against UVA and UVB sunburn\textsuperscript{1}.

EGCG may prevent oxidation and apoptosis of neurons, which may protect people from developing Alzheimer's disease\textsuperscript{42}.

Green tea is an antioxidant, thereby reduces oxidative DNA damage, lipid peroxidation and free radical generation\textsuperscript{43}.

Green tea may reduce mutagenic activity in smokers\textsuperscript{44}.

The tannins may have antidiarrheal properties\textsuperscript{45}.

The polyphenols increase levels of lactobacilli and bifidobacteria, and reduce levels of enterobacteriaceae\textsuperscript{46}.

Through caffeine preventing adenosine's inhibition of dopaminergic transmission, green tea may reduce the clinical expression of Parkinsonism\textsuperscript{47}. 

Green tea may have antiplatelet activity$^{3, 48, 49}$.

**Caffeine**

Caffeine is a central nervous system (CNS) stimulant$^{28, 29, 50}$. Caffeine increases blood pressure, heart rate and heart contractility$^{39, 45, 51}$. Caffeine improves cognitive performance$^{10}$. Caffeine stimulates gastric acid secretion$^{50}$. Caffeine is a diuretic$^{50}$.  

**DRUG INTERACTIONS**

Adenosine (Adenocard)$^{52}$

Anticoagulant, Antiplatelet agents$^{3, 48, 49}$

Antipsychotic drugs$^{53, 54}$

Aspirin, Acetaminophen (Tylenol)$^{55}$

Barbiturates$^{56}$

Benzodiazepines$^{52}$

Beta-adrenergic agonists$^{50}$

Chlorpromazine (Thorazine)$^{52}$

Cimetidine (Tagamet)$^{57}$

Clozapine (Clozaril)$^{52, 56, 58}$

Disulfiram (Antabuse)$^{50}$

Ephedrine$^{52}$
Ergotamine (Ergomar)\textsuperscript{50}

Lithium (Eskalith, Lithobid)\textsuperscript{59, 60}

MAO Inhibitors (MAOIs)\textsuperscript{52}

Mexiletine (Mexitil)\textsuperscript{61}

Oral contraceptives\textsuperscript{57}

Phenylpropanolamine (Propagest, Rhindecon)\textsuperscript{52}

Phenytoin (Dilantin)\textsuperscript{52}

Quinolones\textsuperscript{62-64}

Theophylline (Theo-Dur)\textsuperscript{56}

Verapamil (Calan, Isoptin)\textsuperscript{57}

Warfarin (Coumadin)\textsuperscript{48, 65-68}

**PARTS USED**

Leaf bud, leaf, and stem\textsuperscript{1}

**REFERENCES**


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52. Brinker F. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical

53. Lasswell WLJ, al. e. In vitro interaction of neuroleptics and tricylic antidepressants with

54. Kulhanek F, Linde OK, Meisenberg G. Precipitation of Antipsychotic drugs in interaction
with coffee or tea. Lancet 1979; 2:1130.


58. Hagg S, Spigset O, Mjorndal T, Dahlqvist R. Effect of caffeine on clozapine


60. Jefferson JW. Lithium tremor and caffeine intake: two cases of drinking less and shaking


GUGGUL

Commiphora mukul

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Guggal, guggul gum resin, guggulipid, guggulipids, guggulu, guggulsterone, guggulsterones, gum guggal, gum gugglu, gum guggulu, Indian bdellium-tree, mukul myrrh, mukul myrrh tree

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflicting evidence - Hyperlipidemia(^2-8)</td>
<td>B1</td>
</tr>
<tr>
<td>Nodulocystic acne(^9)</td>
<td>C</td>
</tr>
<tr>
<td>Obesity(^10,11)</td>
<td>C</td>
</tr>
<tr>
<td>Rheumatoid arthritis(^12,13)</td>
<td>D</td>
</tr>
<tr>
<td>Osteoarthritis (with gold)(^14,15)</td>
<td>D</td>
</tr>
<tr>
<td>Osteoarthritis(^16)</td>
<td>E</td>
</tr>
</tbody>
</table>

* A number of studies, including randomized controlled trials, reported that guggal has lipid-lowering effects\(^2-8\). A 2003 randomized controlled trial on guggul, however, reported that guggulipid did not appear to improve levels of serum cholesterol in adults with hypercholesterolemia, and might in fact raise levels of LDL-C\(^17\). Given that this contradicts a number of previously published trials, further investigation is required.
**PREGNANCY**

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient(^{18})</td>
<td>4</td>
</tr>
<tr>
<td>Emmenagogue(^{18})</td>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant(^{19,20})</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that guggul was a potential abortifacient and an emmenagogue\(^{18}\). A herbal toxicology and drug interaction compendium and a herb safety compendium reported that guggul was a uterine stimulant\(^{19,20}\).

**LACTATION**

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based literature of guggul being either safe or contraindicated during lactation.

**TOXICITY**

LD\(_{50}\): 1.6g/kg\(^{21}\)

**CONSTITUENTS**

Ketonic steroids\(^{1}\): Z-guggulsterone and E-guggulsterone

Essential oils\(^{22}\): curzerenone, furanodiene-6-one and furanoeudesma-1,3-diene

Resin
PHARMACOLOGY

Guggul extract, also known as guggulipid (usually standardized to 2.5% guggulsterones), is an ethyl acetate extract of the gum resin that contains both Z- and E-guggulsterones. Guggulsterones inhibit the synthesis of cholesterol in the liver and appear to have an antioxidant effect on lipids. Guggul may lower lipoprotein (a) and C-reactive protein.

Guggual is an antagonist ligand for farnesoid X receptor (FXR) where it decreases expression of bile acid-activated genes.

Guggulsterones may have thyroid-stimulating activity where they increase the conversion of T4 to T3. Guggul may have a protective effect against drug-induced myocardial necrosis.

In acne, guggulipid may reduce secretion of sebum and inhibit bacterial metabolism of triglycerides.

Guggul may have anti-inflammatory activity.

Guggul may have antiplatelet and anticoagulant activity.

DRUG INTERACTIONS

Anticoagulant/antiplatelet drugs

Diltiazem

Propranolol

Thyroid drugs

PARTS USED

Gum resin
REFERENCES


HAWTHORN

Crataegus oxycantha, C. cuneata, C. laevigata

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Aubepine, blanca spino, crataegi flos, crataegi folium, crataegi folium cum flore, crataegi fructus, English hawthorn, epine blanche, epine de mai, haagdorn, hagedorn, harthorne, haw, hawthorn extract, hawthorn flower, hawthorne fruit, hawthorn leaf, hawthorne, hedgethorn, may, maybush, maythorn, mehlbeebaum, meidorn, nan shanzha, oneseed hawthorn, shazha, weissdorn

INDICATIONS

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Coronary Artery Disease (Angina)</td>
</tr>
<tr>
<td>Functional cardiovascular disorders (with camphor)</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine activity</td>
</tr>
</tbody>
</table>

A herbal medicine compendium reported that hawthorn has uterine activity and is unsafe during pregnancy. There are no reports in the evidence-based medicine literature of hawthorn being safe or contraindicated during pregnancy.

LACTATION

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>
There are no reports in the evidence-based medicine literature of hawthorn being safe or contraindicated during lactation.

**CONSTITUENTS**

Flavonoids

Procyanidins

Vtixin

Rutin

Hyperoside

**TOXICITY**

LD$_{50}$: 18-24 mL/kg (intravenous) and 18.5-33.8 mL/kg (oral)$^7$-$^9$

Acute toxicity (LD$_{50}$) of isolated flavonoid constituents: 50-2600 mg/kg (intravenous) and 6 g/kg (oral)$^7$-$^9$

**PHARMACOLOGY**

Hawthorn acts on the myocardium by increasing the force of contraction and by lengthening the refractory period$^6$-$^{10}$.

Hawthorn has antiarrhythmic activity by prolonging refractory period of the action potential$^{11}$.

Hawthorn reduces peripheral vascular resistance and oxygen consumption, and increases nerve conductivity$^6$-$^{12}$.

Hawthorn increases coronary blood flow, vasodilation, and has a positive inotropic effects by increasing calcium membrane permeability and inhibiting phosphodiesterase (which increases intracellular CAMP)$^{12}$-$^{13}$.

Hawthorn reduces lipid levels$^1$.

Hawthorn has antibacterial properties$^{14}$.
Hawthorn has spasmolytic and analgesic effects\textsuperscript{14}. Hawthorn may decrease uterine tone and motility\textsuperscript{1}.

**DRUG INTERACTIONS**

Cardiovascular drugs\textsuperscript{5, 15}

CNS depressants\textsuperscript{5, 6}.

Coronary vasodilators\textsuperscript{6}

Digoxin\textsuperscript{6, 15}

**PARTS USED\textsuperscript{1}**

Leaf, fruit and flower

**REFERENCES**


HORSECHESTNUT

*Aesculus hippocastanum*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES\(^1\)

Buckeye, Chestnut, Escine, Hippocastani Cortex, Hippocastani Flos, Hippocastani folium, Hippocastani Semen, Horse Chestnut, Marron Europeen, Spanish Chestnut, Venastat, Venostat, Venostasin Retard

INDICATIONS

Horse chestnut seed extract (HCSE)

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic venous insufficiency(^2)(^{-21}) A</td>
</tr>
</tbody>
</table>

Escin gel (2%) – Topical

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma(^22) B2</td>
</tr>
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</table>

Escin

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative edema and thrombosis(^23, 24) B2</td>
</tr>
</tbody>
</table>

Esculin

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhoids(^25) C</td>
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</table>
PREGNANCY

Horse chestnut seed extract (HCSE)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^{26})</td>
</tr>
</tbody>
</table>

A randomized placebo controlled trial of 52 women with leg edema attributed to pregnancy-induced venous insufficiency failed to observe any serious adverse effects after two weeks\(^{26}\). Subjects received 300mg twice daily of Venostasin\(^{®}\) retard (240-290mg of horse chestnut seed extract (HCSE), standardized to 50mg escin)\(^{26}\).

Unprocessed (raw) horsechestnut preparations

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic - contraindicated in pregnancy and lactation(^{27,28})</td>
</tr>
</tbody>
</table>

Unprocessed (raw) horsechestnut preparations (seed, bark, flower, leaf) can be lethal when ingested\(^ {28}\). In adults, a few chestnuts can cause severe symptoms, while in children, a few chestnuts can be lethal\(^ {27}\). It has been reported that roasting horsechestnut appears to destroy its toxins\(^ {27}\). Unprocessed horsechestnut was not reported in the evidence-based medicine literature as being either contraindicated or safe for use during pregnancy.

LACTATION

Horse chestnut seed extract (HCSE)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based medicine literature of horse chestnut seed extract (HCSE) being either safe or contraindicated during lactation.
Unprocessed (raw) horsechestnut preparations

<table>
<thead>
<tr>
<th>Level</th>
<th>Toxic - contraindicated in pregnancy and lactation(^{27, 28})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Unprocessed (raw) horsechestnut preparations (seed, bark, flower, leaf) can be lethal when ingested\(^{28}\). In adults, a few chestnuts can cause severe symptoms, while in children, a few chestnuts can be lethal\(^{27}\). It has been reported that roasting horsechestnut appears to destroy its toxins\(^{27}\). Unprocessed horsechestnut was not reported in the evidence-based medicine literature as being either contraindicated or safe for use during lactation.

**CAUTION**

Diabetes or glucose intolerance\(^ {29}\)

**CONSTITUENTS**

Triterpene saponins\(^ {1, 29-32}\): triterpene oligoglycosides (escins Ia, Ib, IIA, IIb, IIIa), acylated polyhydroxyoleanene triterpene oligoglycosides (escins IIIb, IV, V, VI), isoscins (Ia, Ib, V)

Sapogenols\(^ {1, 29-32}\): hippocaesulin, baringtogenol-C

Hydroxycoumarin lactone glycoside\(^ {27}\): esculin

Sterols\(^ {1, 29-32}\): stigmasterol, alpha-spinasterol, beta-sitosterol

Fatty acids\(^ {1, 29-32}\): linolenic, palmitic, stearic acids

Flavonoids\(^ {1, 29-32}\)

Tannins\(^ {1, 29-32}\)

Quinines\(^ {1, 29-32}\)

**TOXICOLOGY**

The constituent esculin is associated with significant toxicity\(^ {28}\).
Horse chestnut seed extract (HCSE) which is standardized to escin content should not contain clinically relevant levels of esculin, and thus most toxicities will not be of concern\textsuperscript{28}.

**PHARMACOLOGY**

**Unprocessed (raw) horsechestnut preparations**

Esculin causes neural stimulation and increases antithrombin activity, thereby leading to increased bleeding time\textsuperscript{27}.

Esculin is a mucous membrane irritant\textsuperscript{27}.

**Horse chestnut seed extract (HCSE)**

Escin, the active ingredient in HCSE has anti-exudative and vascular-tightening effects\textsuperscript{30}.

HCSE reduces vascular permeability, reduces the activity of lysosomal enzymes and inhibits the breakdown of glycoacalyx in the capillary walls\textsuperscript{30}.

HCSE contracts canine and human isolated saphenous veins *in vitro*, possibly due to preferential formation of the vasoconstrictive eicosanoid PGF 2-alpha\textsuperscript{33-35}.

HCSE increases femoral venous pressure and flow; decreases the formation of edema and suppresses plasma extravasation and leucocyte emigration into the pleural cavity\textsuperscript{34, 36}.

HCSE has antioxidant effects\textsuperscript{34}.

**DRUG INTERACTIONS**

Hypoglycemic agents\textsuperscript{29}

Anticoagulant/Anti-platelet therapy\textsuperscript{27}

**PARTS CONTAINING TOXINS\textsuperscript{27}**

Seeds, bark, leaves, pericarp of fruit twigs and non-medicinal flowers
REFERENCES


17. Nill HJ, Fischer H. [Comparative investigations concerning the effect of extract of horse chestnut upon the pressure-volume-diagramm of patients with venous disorders]. Arztl Forsch 1970; 24:141-3.


**JUNIPER**

*Juniperus communis*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Common juniper berry, enebro, geniévre, ginepro, *Juniperi fructus*, wacholderbeeren, zimbro

**INDICATIONS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold (with peppermint oil, cajeput oil, eucalyptus oil and</td>
<td>C</td>
</tr>
<tr>
<td>methylquinolinium oil)</td>
<td></td>
</tr>
<tr>
<td>Renoprotective</td>
<td>E</td>
</tr>
<tr>
<td>Antimycobacterial activity</td>
<td>E</td>
</tr>
<tr>
<td>Hypoglycemic</td>
<td>E</td>
</tr>
<tr>
<td>Antibacterial and antifungal</td>
<td>E</td>
</tr>
<tr>
<td>Diuretic and aquaretic</td>
<td>F</td>
</tr>
<tr>
<td>Cystitis</td>
<td>F</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortifacient</td>
<td>3</td>
</tr>
<tr>
<td>Blocks progesterone production</td>
<td>3</td>
</tr>
</tbody>
</table>

Juniper was reported to cause abortions in pregnant cattle. Isocupressic acid is believed to be the primary abortifacient compound in juniper. Cows feed juniper needles subsequently aborted after 3 to 4 days. Other studies on isocupressic acid have also shown that it has an abortive
effect in pregnant cattle\textsuperscript{11,12}. A review article on the potential value of plants as sources of anti-fertility agents reported that juniper was an abortifacient\textsuperscript{13}.

Isocupressic acid was reported to block progesterone production in bovine luteal cells\textsuperscript{14}. It was concluded that isocupressic acid can induce pregnant cows to abort partly through blocking luteal function\textsuperscript{14}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-implantation activity and interferes with fertility\textsuperscript{15-18}</td>
</tr>
</tbody>
</table>

A study on the anti-implantation activity in female albino rats of a number of herbs found that juniper had 60-70\% anti-implantation activity\textsuperscript{16}. An editorial review of contraceptive products reported that the Drug Research Institute in Lucknow, India, US National Institutes of Health, the World Health Organization, and the Indian Council of Medical Research confirm that juniper has anti-implantation effects\textsuperscript{15}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue\textsuperscript{13}</td>
</tr>
<tr>
<td>Uterine stimulant\textsuperscript{17,18}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that juniper was an emmenagogue\textsuperscript{13}. A herbal toxicology and drug interaction compendium and a herbal medicine compendium reported that juniper is a uterine stimulant\textsuperscript{17,18}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cross into breast milk\textsuperscript{19}</td>
</tr>
</tbody>
</table>

Supplementing rabbit does with aromatic juniper berries before and after pregnancy led offsprings to have a preference for juniper berries in their diet\textsuperscript{19}. The authors theorized that this may imply a transfer of the preference from mother to offspring through breast feeding\textsuperscript{19}.
CONTRAINDICATIONS

Nephritis\textsuperscript{17}

Pyelitis\textsuperscript{17}

CAUTION

Avoid use for more than four weeks without medical advice\textsuperscript{17}

Topical use over large skin wounds or in individuals with acute skin conditions\textsuperscript{20}

Some authors report that long term use of juniper may cause convulsions or kidney damage\textsuperscript{21, 22}, other report that it is non-toxic\textsuperscript{23}.

CONSTITUENTS

Volatile monoterpenes\textsuperscript{7, 17}: alpha-pinene, beta-pinene, beta-myrcene

Volatile alcohol\textsuperscript{17, 18}: terpinen-4-ol

Isocupressic acid\textsuperscript{9}

TOXICITY

LD\textsubscript{50} of juniper extract in mice (intraperitoneal injection): 3g/kg\textsuperscript{24}

LD\textsubscript{50} of juniper oil in rats (oral): 6.28g/kg\textsuperscript{17}

LD\textsubscript{50} of terpinen-4-ol in mice and rats (intramuscular): 0.78 and 1.5ml/kg, respectively\textsuperscript{17}

PHARMACOLOGY

Animal studies have found that juniper oil did not induce changes in function or morphology of the kidneys and was reported as nontoxic\textsuperscript{23}.

The diuretic action of juniper is attributed to the terpinen-4-ol portion which is purported to stimulate glomerular filtration\textsuperscript{18, 25}.

The volatile monoterpenes are irritant to the urinary mucosa\textsuperscript{17}.
Studies have identified isocupressic acid as the primary abortifient compound in juniper\textsuperscript{9}. \textit{In vitro} and \textit{in vivo} studies have shown isocupressic acid is rapidly metabolized to agathic acid, dihydroagathic acid, and tetrahydroagathic acid\textsuperscript{9}.

Juniper demonstrated hypoglycemic activity in both rats and mice\textsuperscript{26,27}.

Juniper was shown to have antifungal, antiviral (against herpes simplex virus 1) and anti-inflammatory properties\textsuperscript{6,18}.

Oral administration of an extract of juniper berries was seen to decrease experimentally-induced foot edema in rats\textsuperscript{28}.

Juniper oil was found to inhibit the growth of \textit{Mycobacterium tuberculosis} and \textit{Mycobacterium avium}\textsuperscript{4}.

**DRUG INTERACTIONS\textsuperscript{1}**

Antidiabetes drugs\textsuperscript{18}

Diuretics\textsuperscript{8,18}

**PARTS USED\textsuperscript{1,17}**

Berries and oil

**REFERENCES**


KAVA

*Piper methysticum*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Ava, ava pepper, ava root, awa, gea, gi, intoxicating long pepper, intoxicating pepper, kao, kava kava, kava-kava, kava-kava root, kava pepper, kava root, kavain, kavapipar, kawa, kawa kawa, kawa-kawa, kawa pepper, kawapfeffer, kew, long pepper, Maori kava, malohu, maluk, meruk, milik, rauschpfeffer, rhizome di kava-kava, sakau, tonga, wurzelstock, yagona, yangona, yaqona, yonga

INDICATIONS

<table>
<thead>
<tr>
<th>Anxiety^2-4</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>May be hepatotoxic (rare)^5-9</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
</tr>
</tbody>
</table>

Although there are 68 case reports of hepatotoxicity related to kava^5,8,9^, recent systematic reviews have concluded that only 2 of the original documented cases can be directly linked to kava^6,7^. A systematic review concluded that the hepatotoxicity observed was likely an immunologically mediated idiosyncratic mechanism, rather than a direct toxic mechanism^7^.

<table>
<thead>
<tr>
<th>May cause loss of uterine tone^10,11</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety unknown</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
A herbal monograph and a herbal toxicology and drug interaction compendium report that kava may cause loss of uterine tone during pregnancy\textsuperscript{10,11}. There are no reports in the evidence-based scientific literature of kava being either safe or contraindicated during pregnancy.

**LACTATION**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cross into breastmilk\textsuperscript{10}</td>
<td>4</td>
</tr>
<tr>
<td>Safety unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

A herbal monograph reported that the pyrone constituents may cross into breast milk with unknown effects\textsuperscript{10}. There are no reports in the evidence-based scientific literature of kava being either safe or contraindicated during lactation.

**CONTRAINDICATION**

Existing liver disease\textsuperscript{12}

Parkinson’s disease\textsuperscript{12}

Existing pulmonary disease\textsuperscript{12}

**CAUTION**

Avoid long term use\textsuperscript{12}

Avoid daily doses above 300 mg\textsuperscript{12}

Operating heavy machinery\textsuperscript{12}

Endogenous depression\textsuperscript{10,13}

**CONSTITUENTS**

Kavalactones (also called kavapyrones)\textsuperscript{14,15}: methysticin, dihydromethysticin (DMH), yangonin, dihydrokavain (DHK), kawain (kavalin)
TOXICITY

LD$_{50}$ of kavalactones: approximately 300-400mg/kg$^{16}$

LD$_{50}$ (oral) of dihydrokavain: 920mg/kg$^{16}$

LD$_{50}$ (oral) of dihydromethysticin: 1050mg/kg$^{16}$

LD$_{50}$ of standardized kava extract (containing 70% kava lactones): 16g/kg (oral, rats), 1.8 g/kg (oral, mice), 370mg/kg (intraperitoneal, rats) and 380mg/kg (intraperitoneal, mice)$^{17}$

Doses of 50mg/kg of dihydrokavain three times a week for 3 months to rats produced no evidence of chronic toxicity$^{18}$.

PHARMACOLOGY

People consuming kava have reported feeling more sociable, tranquil and generally happy$^{19}$.

Kava’s sedative effects may result from an increase in the number of GABA binding sites$^{15,20,21}$.

Kava’s sedative effects may also result from dopamine antagonism, particularly by the vangonin constituent$^{22-25}$.

The kavapyrones methycystine and kavain may inhibit the uptake of noradrenaline, thereby contributing to the psychotrophic actions of kava$^{22}$.

Kava has not been shown to affect benzodiazepine receptors$^{26,27}$.

Kava may affect the limbic system$^{28}$.

Kava appears to produce motor sedation without affecting respiratory processes$^{29}$.

Kava may cause muscle paralysis and numb the mouth through a mechanism similar to local anesthetics such as cocaine$^{19,30}$.

The kavapyrones desmethoxyyangonin and methysticin appear to competitively inhibit monoamine oxidase B (MAO-B)$^{31}$.

Kava may inhibit enzymes in the COX-1 and COX-2 pathways$^{32}$.
The kavapyrone kavain inhibits cyclooxygenase and decreases the synthesis of thromboxane A2, thereby decreasing platelet aggregation\textsuperscript{33}.

Kava may affect the following cytochrome P450 enzymes: P450 2C19 (CYP2C19), P450 1A2 (CYP1A2), P450 2C9 (CYP2C9), P450 2D6 (CYP2D6) and P450 3A4 (CYP3A4)\textsuperscript{34}

**DRUG INTERACTIONS\textsuperscript{1}**

Alprazolam\textsuperscript{35}

Anticoagulant/anti-platelet drugs\textsuperscript{33}

Central nervous system (CNS) depressants\textsuperscript{4, 36}

Drugs metabolized by cytochrome P450 2C19 (CYP2C19), P450 1A2 (CYP1A2), P450 2C9 (CYP2C9), P450 2D6 (CYP2D6) and P450 3A4 (CYP3A4)\textsuperscript{34}

Hepatotoxic drugs\textsuperscript{5, 8}

Levodopa (Larodopa, Dopar)\textsuperscript{37}

Monoamine oxidase inhibitors\textsuperscript{31}

**PARTS USED\textsuperscript{1}**

Rhizome, root and stem

**REFERENCES**


## LEMON BALM

*Melissa officinalis*

### SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Balm, cure-all, dropsy plant, honey plant, melissa, *Melissae folium*, melissenblatt, sweet balm, sweet mary

### INDICATIONS

Lemon balm extract

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate Alzheimer’s disease[^2-4]</td>
<td>B1</td>
</tr>
<tr>
<td>Cold sores (herpes labialis)[^5,6]</td>
<td>B2</td>
</tr>
<tr>
<td>Sleep quality and quantity (with valerian)[^7]</td>
<td>B2</td>
</tr>
<tr>
<td>Dyspepsia (with bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, angelica root, celandine herbs and milk thistle fruit)[^8]</td>
<td>B2</td>
</tr>
<tr>
<td>Chronic colitis (with <em>Taraxacum officinale</em>, <em>Hypericum perforatum</em>, <em>Calendula officinalis</em> and <em>Foeniculum vulgare</em>)[^9]</td>
<td>C</td>
</tr>
<tr>
<td>Anti-ulcerogenic[^10]</td>
<td>E</td>
</tr>
</tbody>
</table>

Oil

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
</table>
PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
<th>Emmenagogue&lt;sup&gt;12&lt;/sup&gt;</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>Hormonal changes&lt;sup&gt;13&lt;/sup&gt;</td>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that lemon balm was an emmenagogue<sup>12</sup>. A herbal toxicology and drug interaction compendium reported that lemon balm causes hormonal changes<sup>13</sup>.

| Level | Antigenadotrophic activity<sup>12</sup> | 4 |

A review article on the potential value of plants as sources of anti-fertility agents reported that lemon balm had antigenadotrophic activity in rats<sup>12</sup>.

LACTATION

| Level | Hormonal changes<sup>13</sup> | 4 |

A herbal toxicology and drug interaction compendium reported that lemon balm causes hormonal changes<sup>13</sup>. There are no reports in the evidence-based medicine literature of lemon balm being either safe or contraindicated during lactation.

CONSTITUENTS

Monoterpenoid aldehydes<sup>1</sup>: citronellal, neral, and geranial

Polyphenolic compounds<sup>14</sup>: rosmarinic acid

Flavonoids<sup>15</sup>: Luteolin 3'-O-beta-D-glucuronide
PHARMACOLOGY

Lemon balm induces a calming effect and reduces alertness\textsuperscript{16}.

*In vitro* lemon balm extracts have cholinergic binding properties and may effectively ameliorate the cognitive deficits associated with Alzheimer's disease\textsuperscript{16}.

Lemon balm may have nicotinic and muscarinic binding properties\textsuperscript{16}.

The terpenes in the essential oil of lemon balm are rapidly absorbed through the lungs and cross the blood-brain barrier, and may have cholinergic activity or act on gamma-aminobutyric acid (GABA) receptors\textsuperscript{17}.

Lemon balm was shown to have anti-herpes simplex 1 activity and antiviral effects\textsuperscript{18-20}.

Lemon was shown to have anti-HIV-1 activity\textsuperscript{21}.

Rosmarinic acid may have antithyroid effects\textsuperscript{22}.

Rosmarinic acid may have anti-inflammatory activity through its inhibitory effects on complement C3-convertase\textsuperscript{14}.

Lemon balm was shown to have protective effects against enzyme dependent and independent lipid peroxidation\textsuperscript{23}.

DRUG INTERACTIONS\textsuperscript{1}

Barbiturates\textsuperscript{16}

Sedative drugs\textsuperscript{16}

Thyroid hormone\textsuperscript{22}

PARTS USED\textsuperscript{1}

Leaf, oil
REFERENCES


LICORICE

*Glycyrrhiza glabra*

**SYNONYMS/COMMON NAMES/RELATED COMPOUNDS**


**INDICATIONS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion (with bitter candy, chamomile, peppermint, caraway, lemon balm, angelica, celandine, milk thistle)</td>
<td>B2</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura (with corticosteroids)</td>
<td>B2</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>B2</td>
</tr>
<tr>
<td>Familial Mediterranean Fever (with andrographis, Siberian ginseng, schizandra)</td>
<td>B2</td>
</tr>
<tr>
<td>Hemophiliacs with HIV-1</td>
<td>C</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>C</td>
</tr>
<tr>
<td>Viral hepatitis (with interferon)</td>
<td>C</td>
</tr>
<tr>
<td>Oral lichen planus</td>
<td>C</td>
</tr>
<tr>
<td>Dental plaque</td>
<td>C</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>C</td>
</tr>
</tbody>
</table>
Herpes zoster\textsuperscript{18} & D \\
Psoriasis (with \textit{Tripterygium wilfordii} and \textit{Erythromycia})\textsuperscript{19} & D \\

Deglycyrrhizinated licorice (DGL) & \\

| Aphthous ulcers\textsuperscript{20} & C \\
| Gastric and duodenal ulcers\textsuperscript{21-23} & E \\
| Gastric mucosal damage by acetyl salicylic acid (Aspirin)\textsuperscript{24} & E |

**PREGNANCY**

| Likely to be born before 38 weeks gestation\textsuperscript{25} & 1b \\
| Risk of pre-term pregnancy (before 37 weeks)\textsuperscript{26} & 1b \\
| Does not affect birth weight\textsuperscript{25} & 1b \\
| Does not affect maternal blood pressure\textsuperscript{25} & 1b |

A study of 1,049 Finnish women found babies with heavy exposure to glycyrrhizin were significantly more likely to be born earlier\textsuperscript{25}. The odds ratio for being born before 38 weeks' gestation was 2.5\textsuperscript{25}. They also reported that heavy glycyrrhizin exposure during pregnancy did not significantly affect birth weight or maternal blood pressure\textsuperscript{25}. Another study of 95 women found that heavy consumption of glycyrrhizin was associated with a more than twofold increased risk of preterm (<37 weeks) delivery\textsuperscript{26}.

| Minimal risk\textsuperscript{27} & 1c |
A study published 110 case reports on the use of glycyrrhizin injections for the treatment of viral hepatitis during pregnancy\textsuperscript{27}. No adverse effects were reported\textsuperscript{27}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogenic\textsuperscript{28, 29}</strong></td>
</tr>
</tbody>
</table>

The constituent glabridin was shown to have varying degrees of estrogen receptor agonism in different tests and demonstrated growth-inhibitory actions on human breast cancer cells\textsuperscript{28}. A review article on the potential value of plants as sources of anti-fertility agents reported that licorice has estrogenic activity\textsuperscript{29}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential abortifacient\textsuperscript{30}</strong></td>
</tr>
<tr>
<td><strong>Emmenagogue\textsuperscript{30}</strong></td>
</tr>
<tr>
<td><strong>Uterine stimulant\textsuperscript{30}</strong></td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that licorice was a potential abortifacient, emmenagogue and uterine stimulant\textsuperscript{30}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causes high prolactin and estrogen levels\textsuperscript{31, 32}</strong></td>
</tr>
</tbody>
</table>

An evidence-based herbal monograph reported that licorice causes high prolactin levels and high estrogen levels in women\textsuperscript{31, 32}.

Deglycyrrhizinated licorice (DGL)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unknown</strong></td>
</tr>
</tbody>
</table>
It is unknown if the removal of the glycyrrhizin constituent in licorice makes DGL safe during pregnancy. There are no reports in the evidence-based scientific literature of DGL being either safe or contraindicated during pregnancy.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
<th>Hormonal effects(^{31,32})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

An evidence-based herbal monograph reported that licorice causes high prolactin levels and high estrogen levels in women\(^{31,32}\). There are no reports in the evidence-based scientific literature of licorice being either safe or contraindicated during lactation.

Deglycyrrhizinated licorice (DGL)

<table>
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<th>Level</th>
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</table>

It is unknown if the removal of the glycyrrhizin constituent in licorice makes DGL safe during lactation. There are no reports in the evidence-based scientific literature of DGL being either safe or contraindicated during lactation.

**CONTRAINDICATIONS**

- Long-term use\(^{32}\)
- Hypertension\(^{32}\)
- Hypokalemia\(^{32}\)
- Cardiovascular disease\(^{32}\)
- Diabetes\(^{32}\)
- Liver disorders (cholestasis, chronic hepatitis, cirrhosis)\(^{32}\)
- Severe kidney insufficiency\(^{32}\)
CONSTITUENTS

Triterpenoid saponins: glycyrrhizin (glycyrrhizic acid), glycyrrhetinic acid (18-beta-glycyrrhetinic acid)

Flavonoids: liquiritin, chalcones and isoflavonoids

Sterols

TOXICITY

No significant changes were observed in rats fed 100-1000 mg/kg per day for 1 year (intragastric route).

Glycyrrhizin

Long-term administration of glycyrrhizin did not induce tumours in mice.

Glycyrrhetinic acid

In rats, oral consumption of glycyrrhetinic acid caused an increase in right atrial pressure and thickening of the pulmonary vessels, suggesting pulmonary hypertension.

In patients with previous breast cancer, doses of 0.02-0.03 mmol/kg of glycyrrhetinic acid experienced hypertension or hypokalemia, which required dose reduction or discontinuance.

PHARMACOLOGY

Glycyrrhizin contributes to the mineralocorticoid effects of licorice, such as hypertension and hypokalemia, by binding directly to mineralocorticoid receptors and by decreasing the conversion of active cortisol to inactive cortisone.

The constituents glycyrrhizin and glycyrrhetinic acid inhibit the enzyme 11-beta-hydroxysteroid dehydrogenase, which is located in the aldosterone receptor cells of the cortical collecting duct.
Licorice blocks the metabolism of prostaglandins E and F2 alpha, which may have a preventative effect on non-steroidal anti-inflammatory drugs (NSAIDs)-induced damage to the gastrointestinal (GI) mucosa\textsuperscript{52}.

Licorice appears to have anti-estrogenic and estrogenic activity, where the constituent glabridin has estrogenic activity at low concentrations and anti-estrogenic activity at high concentrations\textsuperscript{28}.

Licorice does not appear to stimulate the growth of estrogen dependent breast cancer cells\textsuperscript{53}.

Intravenous preparations of glycyrrhizin and glycyrrhizic acid were shown to have activity against hepatitis B and C in humans\textsuperscript{13, 14, 54}.

Licorice may decrease testosterone production in young healthy men\textsuperscript{55}.

Licorice may reduce body fat, but the accompanying fluid retention offsets any change in body weight\textsuperscript{56}.

Deglycyrrhizinated licorice (DGL)

Deglycyrrhizinated licorice (DGL) may accelerate the healing of gastric and duodenal ulcer disease\textsuperscript{21-23}.

**DRUG INTERACTIONS\textsuperscript{1}**

Antihypertensive drugs\textsuperscript{57}

Corticosteroids\textsuperscript{52, 58}

Drugs metabolized by cytochrome P450 3A4 and P450 2B6\textsuperscript{59, 60}

Digoxin\textsuperscript{52}

Potassium-depleting diuretic drugs\textsuperscript{58}

Estrogens\textsuperscript{51}

Ethacrynic acid\textsuperscript{61}

Furosemide\textsuperscript{61}
Insulin

PARTS USED

Root

References


46. Hussain RM. The sweet cake that reaches parts other cakes can't! Postgrad Med J 2003; 79:115-6.


**MILK THISTLE**

*Silybum marianum*

**Synonyms/Common Names/Related Substances**

Holy Thistle, Lady's Thistle, Legalon, *Cardui mariae fructus, Cardui mariae herba*, Marian Thistle, Mariendistel, Mary Thistle, Our Lady's Thistle, St. Mary Thistle, Silybin, Silybum, Silymarin

**INDICATIONS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Alcoholic liver cirrhosis&lt;sup&gt;2-6&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Liver cirrhosis mortality&lt;sup&gt;2,4&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Non-alcoholic liver cirrhosis&lt;sup&gt;4,7&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Chronic viral hepatitis C&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Acute viral hepatitis&lt;sup&gt;10&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Diabetes mellitus-related cirrhosis&lt;sup&gt;2,11,12&lt;/sup&gt;</td>
<td>B1</td>
</tr>
<tr>
<td>Drug induced liver toxicity&lt;sup&gt;13&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Dyspepsia (with bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, angelica root, celandine herbs and lemon balm)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>B2</td>
</tr>
<tr>
<td>Toxicity-induced liver disease&lt;sup&gt;15,16&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td>Diabetes mellitus Type 2&lt;sup&gt;17&lt;/sup&gt;</td>
<td>C</td>
</tr>
<tr>
<td><em>Amanita phalloides</em> mushroom poisoning&lt;sup&gt;2,18,19&lt;/sup&gt;</td>
<td>D</td>
</tr>
</tbody>
</table>
Primarily fatty degeneration of the liver \(^20\)  & D \\
Hepatocellular carcinoma \(^21\)  & E \\
Cancer prevention \(^22, 23\)  & E \\

**PREGNANCY**

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Minimal risk (^24-26)  &amp; 1a</td>
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</table>

A 60-day trial of silymarin 400mg daily was conducted in pregnant women and adults with “minor liver insufficiencies” \(^24\). No adverse effects were reported in the mothers and offspring \(^24\).

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Treatment of intrahepatic cholestasis of pregnancy (^25-27)  &amp; 1c</td>
</tr>
<tr>
<td>Minimal risk (^25-27)  &amp; 1c</td>
</tr>
</tbody>
</table>

When administered to a small group of patients over 15 days, milk thistle was shown to attenuate pruritis in pregnant women with intrahepatic cholestatis of pregnancy \(^25-27\). No adverse effects were reported with the use of milk thistle \(^25-27\).

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Emmenagogue (^28)  &amp; 4</td>
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<tr>
<td>Uterine stimulant constituent (^28)  &amp; 4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that milk thistle was an emmenagogue and that it contains the uterine stimulant constituent tyramine \(^28\).
**LACTATION**

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<th>Grade</th>
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</table>

Milk thistle was not reported in the evidence-based medicine literature as being contraindicated or safe during lactation.

**CONSTITUENTS**

Flavonolignans\(^{29,30}\): Silybin A and B, Silydistin, Silydianin, Silymarin, Silibinin

Tyramine\(^{28}\)

**PHARMACOLOGY**

Silybin, a milk thistle constituent, was shown to stimulate RNA polymerase A and DNA synthesis\(^{31}\). This stimulation increases the synthesis of ribosome proteins, stimulates cell development and thereby increases the regenerative capacity of the liver\(^{31}\).

Regular consumption of standardized preparations of milk thistle were shown to control the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT)\(^{8,32}\).

Silymarin, the active constituent in milk thistle, may competitively bind some toxins and act as a free radical scavenger\(^{33,34}\).

Silymarin may increase the hepatic contents of glutathione (both oxidized and reduced)\(^{35}\).

Silymarin may increase the enzyme superoxidase dismutase (SOD)\(^{36}\).

Silymarin may regulate cell membrane permeability, inhibit the 5-lipoxygenase pathway, scavenge for reactive oxygen species (ROS) of the R-OH type and effect DNA-expression\(^{2}\).

Silibinin, a constituent of milk thistle, was shown to significantly inhibit cell growth and DNA synthesis of different prostate, breast and cervical human carcinoma cells\(^{22}\).
Silibinin treatment significantly decreased both intracellular and secreted forms of prostate specific antigen (PSA) and inhibited cell growth via a G1 arrest in cell cycle progression\textsuperscript{23}. Milk thistle may affect cytochrome P450 2C9 (CYP2C9) and P450 3A4 (CYP3A4)\textsuperscript{40,41}.

**DRUG INTERACTIONS**

Estrogens\textsuperscript{37}

Glucuronidated drugs\textsuperscript{38,39}

Drugs metabolized by cytochrome P450 2C9 (CYP2C9) and P450 3A4 (CYP3A4)\textsuperscript{40,41}

**PART USED\textsuperscript{29}**

Seeds

**References**


STINGING NETTLE

_Urtica dioica, Urtica urens_

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Common nettle, dwarf nettle, great stinging nettle, nettle, nettles, ortie, small nettle, urtica, _Urticae herba et folium_

INDICATIONS

Aboveground parts

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Allergic rhinitis³</td>
<td>B2</td>
</tr>
<tr>
<td>Osteoarthritis⁴,⁵</td>
<td>B2</td>
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</tbody>
</table>

Root

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<thead>
<tr>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Benign prostatic hyperplasia (with saw palmetto)⁶,⁷</td>
<td>B1</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia⁸</td>
<td>B2</td>
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PREGNANCY

Aboveground parts

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Potential Abortifacient⁹</td>
<td>4</td>
</tr>
<tr>
<td>Emmenagogue⁹</td>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant constituent⁹</td>
<td>4</td>
</tr>
</tbody>
</table>
A review article on the potential value of plants as sources of anti-fertility agents reported that stinging nettle was a potential abortifacient, emmenagogue and that its constituent, 5-hydroxytryptamine, was a uterine stimulant. This review article also reported that stinging nettle has estrogenic activity.

**Root**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Interferes with human sex hormone-binding globulin</td>
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<td>3</td>
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</table>

Stinging nettle root has been shown to interfere with human sex hormone-binding globulin. The root is principally used in the treatment of prostate disorders and as such, would not likely be used during pregnancy. There are no reports in the evidence-based scientific literature of stinging nettle root being either safe or contraindicated during pregnancy.

**LACTATION**

Aboveground parts

<table>
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There are no reports in the evidence-based scientific literature of stinging nettle leaf being either safe or contraindicated during lactation.

**Root**

<table>
<thead>
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<tbody>
<tr>
<td>Interferes with human sex hormone-binding globulin</td>
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Stinging nettle root has been shown to interfere with human sex hormone-binding globulin. The root is principally used in the treatment of prostate disorders and as such, would not likely...
be used during lactation. There are no reports in the evidence-based scientific literature of stinging nettle root being either safe or contraindicated during lactation.

**CONSTITUENTS**

Leaf\(^1,\,2,\,12-16\): beta-sitosterol, flavonoids (quercetin, rutin, kaempferol), carotene, vitamin C, vitamin K, potassium, calcium, chlorophyll, 5-hydroxytryptamine

Root\(^1\): Polysaccharides

**TOXICITY**

LD\(_{50}\) (leaf infusion): 1.92g/kg\(^4\)

LD\(_{50}\) (leaf decoction): 1.72g/kg\(^4\)

The stinging nettle hairs on the leaf contain histamine, acetylcholine and serotonin; these hairs cause skin irritation when touched\(^13-15,\,17-19\).

**PHARMACOLOGY**

Aboveground parts

Stinging nettle leaf has analgesic, anti-inflammatory, local anesthetic, hemostatic, antibacterial, antiviral, and hyperglycemic effects\(^1,\,13,\,16,\,18-20\).

Stinging nettle contains the uterotrophic constituent 5-hydroxytryptamine\(^2\).

The constituent quercetin decreases histamine release from basophils and mast cells\(^21\).

The leaf has been shown to have diuretic properties where it increases urine output and to slightly decrease systolic blood pressure and body weight in people with venous insufficiency\(^13,\,18\).

Stinging nettle may inhibit adrenergic stimulation, tumor necrosis factor (TNF), and platelet activation factor (PAF)\(^18\).
Stinging nettle lowers body temperature and may act as a central nervous system depressant\textsuperscript{13, 19, 20}.

Stinging nettle may have anti-seizure activity\textsuperscript{19}.

Stinging nettle may decrease blood pressure and heart rate\textsuperscript{18, 19}.

Stinging nettle contains a large amount of vitamin C and carotene\textsuperscript{17}.

Root

Stinging nettle root has immuno-modulating and weak anti-inflammatory properties\textsuperscript{15, 18, 22}.

Root extracts have been shown to decrease binding capacity of sex hormone binding globulin and to suppress prostatic cell metabolism\textsuperscript{14, 18, 22}.

Root extracts have been shown to increase urine output, decreased nocturia, and decreased urinary frequency\textsuperscript{12, 13, 18, 20, 22}.

**DRUG INTERACTIONS\textsuperscript{1}**

Anticoagulants\textsuperscript{16}

Antidiabetic drugs\textsuperscript{19}

Antihypertensive agents\textsuperscript{19}

Central nervous system (CNS) depressants\textsuperscript{19}

**PARTS USED\textsuperscript{1}**

Above ground parts, leaf

**REFERENCES**


OREGON GRAPE

*Berberis aquifolium*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Blue barberry, creeping barberry, holly barberry, holly-leaved berberis, holly mahonia, mountain-grape, Oregon barberry, Oregon grape-holly, scraperoof, trailing mahonia, water-holly

INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Chloroquine-resistant malaria (with pyrimethamine) (^2)</td>
<td>B1</td>
</tr>
<tr>
<td>Infectious diarrhea (^3,4)</td>
<td>B1</td>
</tr>
<tr>
<td>Trachoma ((Chlamydia trachomatis eye infection)) (^5,6)</td>
<td>B2</td>
</tr>
<tr>
<td>Psoriasis (topical) (^7,8)</td>
<td>C</td>
</tr>
<tr>
<td>Congestive heart failure (^9)</td>
<td>C</td>
</tr>
<tr>
<td>Upper respiratory tract infections (^10,11)</td>
<td>E</td>
</tr>
<tr>
<td>Anti-<em>Helicobacter pylori</em> (^12)</td>
<td>E</td>
</tr>
<tr>
<td>Cancer prevention (^13-15)</td>
<td>E</td>
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PREGNANCY

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<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>May cause newborn jaundice (kernicterus) (^16)</td>
<td>3</td>
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</tbody>
</table>

In rats, berberine displaces bilirubin bound to albumin\(^16\). Berberine (10-20 ug/g) was administered intraperitonealy to adult rats on a daily basis for 1 week\(^16\). After one week, a significant decrease in mean bilirubin serum protein binding was observed, due to an *in vivo*
displacement effect by berberine\textsuperscript{16}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{16}.

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<tr>
<td>Uterine stimulant\textsuperscript{17,18}</td>
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A review article on the potential value of plants as sources of anti-fertility agents reported that Oregon grape contains the uterine stimulant berberine\textsuperscript{17,18}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>May cause or aggravate newborn jaundice (kernicterus)\textsuperscript{16}</td>
</tr>
</tbody>
</table>

In rats, berberine displaces bilirubin bound to albumin\textsuperscript{16}. Berberine (10-20 ug/g) was administered intraperitonealy to adult rats on a daily basis for 1 week\textsuperscript{16}. After one week, a significant decrease in mean bilirubin serum protein binding was observed, due to an \textit{in vivo} displacement effect by berberine\textsuperscript{16}. A persistent elevation in serum concentrations of unbound and total bilirubin was also observed\textsuperscript{16}.

**CONTRAINDICATION**

Newborn jaundice (kernicterus)\textsuperscript{16}

**TOXIC CONSTITUENTS**

Isoquinoline alkaloids\textsuperscript{19,20}: oxyacanthine, berbamine, berberine

**TOXICOLOGY**

LD\textsubscript{50} of berberine in humans\textsuperscript{17}: 27.5 mg/kg
PHARMACOLOGY

Berberine was found to displace bilirubin bound to albumin in vitro\textsuperscript{16}. Berberine was found to be about ten times superior to phenylbutazone, a known potent displacer of bilirubin, and about one hundred times superior to papaverine, a berberine-type alkaloid\textsuperscript{16}.

The constituents berberine and oxyacanthine have been shown to have antibacterial activity\textsuperscript{10,11,21,22}.

Berberine has been shown to have amebicidal, anti-parasitic (trypanocidal) and anti-fungal activity\textsuperscript{21,23-25}.

Berberine and beta-hydrastine were shown to have anti-\textit{Helicobacter pylori} activity in vitro\textsuperscript{12}.

In low doses, berberine may act as a cardiac and respiratory stimulant, while in high doses it may act as a cardiac and respiratory depressant\textsuperscript{17,19,21}.

Berberine was shown to have anti-platelet activity\textsuperscript{26}.

Berberine, oxyacanthine and barbamine were shown to have anti-inflammatory effects\textsuperscript{27-30}.

Berberine was found to have an antidiarrheal effects\textsuperscript{31}.

Berberine was found to inhibit parathyroid hormone (PTH)-stimulated bone resorption, inhibit osteoclastic bone resorption and prevent a decrease in bone mineral density of the lumbar vertebra\textsuperscript{32}.

DRUG INTERACTIONS

Anticoagulant drugs\textsuperscript{26}

Highly protein bound drugs\textsuperscript{16}.

PARTS USED\textsuperscript{1}

Root and rhizome
References


Methoxyhydnocarpin-D and pheophorbide A: Berberis species components that potentiate

12. Mahady GB, Pendland SL, Stoia A, Chadwick LR. In vitro susceptibility of Helicobacter
pylori to isoquinoline alkaloids from Sanguinaria canadensis and Hydrastis canadensis.

13. Anis KV, Rajeshkumar NV, Kuttan R. Inhibition of chemical carcinogenesis by berberine

14. Chung JG, Chen GW, Hung CF, et al. Effects of berberine on arylamine N-
acetyltransferase activity and 2-aminofluorene-DNA adduct formation in human leukemia cells.

15. Fukuda K, Hibiya Y, Mutoh M, Koshiji M, Akao S, Fujiwara H. Inhibition by berberine

63:201-8.


18. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HH. Potential value of plants

1999.


21. Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs


KOREAN GINSENG

Panax ginseng, Panax schinseng

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Asian ginseng, Asiatic ginseng, Chinese ginseng, ginseng, ginseng asiaticque, Ginseng radix, ginseng root, guigai, hong shen, Japanese ginseng, jen-shen, jinsao, jintsam, insam, Korean ginseng, Korean panax ginseng, Korean red ginseng, ninjin, Oriental ginseng, Panax ginseng, Radix ginseng rubra, red ginseng, ren shen, renshen, renxian, sang, seng, sheng shai shen, white ginseng

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>B1</td>
</tr>
<tr>
<td>Premature ejaculation</td>
<td>B1</td>
</tr>
<tr>
<td>Diabetes type II</td>
<td>B1</td>
</tr>
<tr>
<td>Improves memory (with Ginkgo biloba)</td>
<td>B1</td>
</tr>
<tr>
<td>Potentiates against influenza and the common cold (with influenza vaccine)</td>
<td>B1</td>
</tr>
<tr>
<td>Improves cognitive function</td>
<td>B2</td>
</tr>
<tr>
<td>Chronic bronchitis (with antibiotics)</td>
<td>C</td>
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<tr>
<td>Cancer prevention</td>
<td>C</td>
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## PREGNANCY

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Level</th>
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<tbody>
<tr>
<td>Conflicting evidence</td>
<td></td>
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<tr>
<td>Non-estrogenic&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1a</td>
</tr>
<tr>
<td>Estrogenic&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2</td>
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</table>

A randomised controlled trial of 384 women receiving either ginseng extract or placebo for 16 weeks showed that the beneficial effects in the treatment of menopause are most likely not mediated by hormone replacement-like effects, as physiological parameters such as FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH were not affected by the treatment<sup>12</sup>.

On the other hand, there are case reports and animal studies of estrogenic activity, postmenopausal vaginal bleeding, increased serum ceruloplasmin oxidase activity and that ginsenoside Rb1 acts as a phytoestrogen<sup>14-20</sup>. A review article on the potential value of plants as sources of anti-fertility agents also reported that Korean ginseng has estrogenic activity<sup>13</sup>.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Level</th>
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<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1b</td>
</tr>
<tr>
<td>Treatment of intrauterine growth retardation&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1b</td>
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A comparison study on pregnant women with intrauterine growth retardation was conducted where one group of women received Korean ginseng while the other group acted as controls<sup>21</sup>. The height of fundus, fetal biparietal diameter, urinary estrogens/creatinine, serum human placental lactogen and neonatal weights approached normal pregnancy values<sup>21</sup>. The authors did not report any adverse effects associated with ginseng supplementation<sup>21</sup>.

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Level</th>
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<tbody>
<tr>
<td>No evidence to support androgenization&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>2</td>
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</tbody>
</table>
A case was reported of a 30-year-old woman who gave birth to a full-term baby boy with signs of androgenization following ingestion of “ginseng” during her pregnancy\(^{23}\). After further investigation, the herbal preparation used by the mother appeared to be adulterated by the herb silk vine (\textit{Periploca sepium}) and not Siberian ginseng (\textit{Eleutherococcus senticosus})\(^{22}\).

<table>
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<tbody>
<tr>
<td>Protects neonatal brain against ethanol damage(^{24})</td>
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<td>3</td>
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</table>

A study reported that ginseng extract prevented ethanol-induced reduction of neonatal brain weight in rats\(^{24}\). The ginseng saponins, including ginsenosides Rg1, Rb2, Rd, Rf and Re, were shown to stimulate a potent recovery of cerebellum growth\(^{24}\).

<table>
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<tr>
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<tbody>
<tr>
<td>Teratogenic(^{25})</td>
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A study on organogenesis found that ginsenosides exert direct teratogenic effects on rat embryos\(^{25}\).

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</thead>
<tbody>
<tr>
<td>Activates DNA polymerase delta in placenta(^{26})</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Ginsenosides from \textit{Panax ginseng} were found to activate DNA polymerase delta in bovine placenta\(^{26}\).

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>May cause neonatal death(^{27})</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

An evidence-based natural product compendium reported that there is one report of neonatal death following use of \textit{Panax ginseng}\(^{27}\). There were no reports in the evidence-based medicine literature of \textit{Panax ginseng} causing neonatal death.
Traditionally used during pregnancy$^{28}$  

Researchers conducted a review of the herbs used during pregnancy in Singapour$^{28}$. Korean ginseng was used in various combinations and in various amounts in herbal prescriptions during pregnancy$^{28}$. The researchers could not confirm that the claims made by Chinese herbalists on the efficacy of Korean ginseng in pregnancy were substantiated$^{28}$. They concluded that there is no specific effect on the pregnant woman, but that it does not exclude the possibility of a beneficial psychosomatic effect$^{28}$. The researchers also noted that the active principles can cross the placenta and reach the fetus$^{28}$. The authors did not discuss if Korean ginseng was safe or contraindicated during pregnancy$^{28}$.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Minimal risk$^{29-31}$</td>
</tr>
</tbody>
</table>

Cows with subclinical mastitis caused by *Staphylococcus aureus* were subjected to subcutaneous injections with an extract from the root of Korean ginseng$^{29}$. Based on blood leukocyte measurements, ginseng treatment was found to activate the innate immunity of cows and contribute to the cow's recovery from mastitis$^{29}$. The authors did not report any adverse effects associated with the use of Korean ginseng during lactation$^{29}$. Two other studies by the same authors conducted in lactating cows found similar results where Korean ginseng increased leukocyte activity and no adverse effects were reported$^{30,31}$.

**CONSTITUENTS**

Triterpenoid Saponins$^{32}$: ginsenosides (Rg1, Rb1)

Polyacetylenic constituents$^{32}$: panaxynol, panaxydol, panaxytriol

Panaxagin$^{33}$
Essential oil
Phytosterol
Pectin
B vitamins
Flavonoids

**TOXICITY**

Very low incidence of toxicity has been observed in ginseng clinical trials using well-characterized preparations.

**PHARMACOLOGY**

Ginseng is frequently used as a general tonic, adaptogen and restorative due to its antifatigue, immunologic and hormonal qualities.

Ginsenosides increase serum cortisol levels, stimulate adrenal function and in women, increase dehydroepiandrosterone sulfate (DHEA-S).

Ginsenoside Rb1 lowers blood pressure and acts as a CNS depressant.

Ginsenosides interfere with platelet aggregation and coagulation.

Ginsenosides have analgesic and anti-inflammatory effects.

Ginsenosides potentiate nerve growth factor and may have a neuroprotective effect through nicotinic activity.

Ginsenosides have anti-asthmatic effects through the relaxation of human bronchial smooth muscle by stimulating the release of nitrous oxide from airway epithelium.

Panax ginseng has anti-tumour activity. The polyacetylenic constituents panaxydol seems to have antiproliferative effects on various types of cancer cells.

Panax ginseng has shown inhibitory activity on Helicobacter pylori.
**Panax ginseng** promotes the growth of normal intestinal flora while inhibiting Clostridial species\(^47\).

**Panax ginseng** may lower cholesterol and triglycerides\(^42\).

**Panax ginseng** may prevent insulin resistance and change gene expression in Type II diabetes\(^48\).

There is conflicting evidence on whether or not *Panax ginseng* has estrogenic activity\(^12,14-20\).

The protein isolate panaxagin may have antiviral and antifungal activity where it appears to inhibit HIV reverse transcriptase and ribosomal activity of some fungi\(^33\).

**Panax ginseng** may mildly inhibit cytochrome P450\(^49\).

**Panax ginseng** increases penile vibratory threshold and reduces the amplitude of penile somatosensory evoked potentials\(^3\).

**DRUG INTERACTIONS**

Anticoagulant/antiplatelet agents\(^50,51\)

Antidiabetics drugs\(^52\)

Antipsychotic drugs\(^53\)

Caffeine\(^54\)

Furosemide\(^55\)

Immunosuppressants\(^11\)

Insulin\(^54\)

Monoamine Oxidase Inhibitors (MAOIs)\(^56,57\)

Stimulant drugs\(^58\)

Warfarin (Coumadin)\(^50,51,59\)

Drugs metabolized by cytochrome P450 enzymes\(^49\)
PARTS USED

Root

REFERENCES


PARSLEY

Petroselinum crispum, P. sativum

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Common parsley, garden parsley, hamburg parsley, persely, persil, petersylinge, Petroselini herba, Petrosilini radix, rock parsley

INDICATIONS

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant activity</td>
<td>B2</td>
</tr>
<tr>
<td>Abortifacient</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

Whole plant

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortifacient</td>
<td>1b</td>
</tr>
</tbody>
</table>

A descriptive retrospective survey was conducted on the calls received by the Montevideo Poison Center between 1986 and 1999 concerning the ingestion of herbal infusions with abortive intent. Parsley was reported as one of the most frequently used herbs for self-induced abortions. The authors also reported that abortion occurred in a number of cases after the ingestion of parsley. Also, there is a 1973 case report of abortion following the ingestion of parsley and naphthalene. A review article on the potential value of plants as sources of anti-fertility agents reported that parsley was a potential abortifacient.
A review article on the potential value of plants as sources of anti-fertility agents reported that parsley was an emmenagogue, uterine stimulant and that its constituent, apiol, was a uterine stimulant\(^5\). This review article also reported that parsley has estrogenic activity\(^6\).

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Emmenagogue(^5)</td>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant constituent(^5)</td>
<td>4</td>
</tr>
<tr>
<td>Estrogenic(^6)</td>
<td>4</td>
</tr>
</tbody>
</table>

Aerial parts

<table>
<thead>
<tr>
<th>Estrogenic activity(^6,7)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
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</tbody>
</table>

Extracts from the aerial parts of parsley showed potent estrogenic activity, which was equal to that of isoflavone glycosides from soybean\(^7\). The methanolic extract of parsley, apiin, and apigenin restored the uterus weight in ovariectomized mice when orally administered for consecutive 7 days\(^7\). A review article on the potential value of plants as sources of anti-fertility agents reported that parsley has estrogenic activity\(^6\).

Myristicin

<table>
<thead>
<tr>
<th>Potentially mutagenic(^8)</th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Liver DNA adducts were detected in fetal liver when pregnant mice were intubated with myristicin\(^8\).
**LACTATION**

Whole plant

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of parsley being either safe or contraindicated during lactation.

Aerial parts

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogenic activity</td>
</tr>
</tbody>
</table>

Extracts from the aerial parts of parsley showed potent estrogenic activity.

**CONTRAINDICATIONS**

Kidney inflammation

**CONSTITUENTS**

Leaf and root: Volatile oils (apiole, myristicin, furanocoumarins (psoralens)), flavone glycosides (apiin, apigenin), carotene, vitamin B1, vitamin B2, vitamin C and vitamin K

Seed: Volatile oils (apiole, myristicin, furanocoumarins (psoralens))

**TOXICITY**

LD$_{50}$ (oral) of volatile oil: 1.52g/kg to 3.96g/kg
PHARMACOLOGY

Leaf and root

Parsley has been reported as having anti-flatulent, antispasmodic, anti-rheumatic, expectorant, antimicrobial and aquaretic (increased urine volume without sodium loss) effects\(^1\),\(^{10-13}\).

Parsley irritates the kidney epithelium which increases renal blood flow and glomerular filtration rate, and consequently, increases urine output\(^10\).

The constituent apiole may stimulate menstrual flow and smooth muscle contractibility in the bladder and intestines\(^14\).

The constituents apiole and myristicin may have aquaretic and uterine stimulant effects\(^10\).

Seed

Parsley seed may stimulate appetite and improve digestion due to its volatile oil content\(^15\).

The volatile oil from the seed has mild aquaretic and laxative properties\(^15\),\(^{16}\).

Parsley seed causes a laxative effect by inhibiting the Na-K pump and by stimulating the NaKCl\(_2\) transporter\(^16\).

Parsley seed oil may stimulate hepatic regeneration\(^11\).

DRUG INTERACTIONS\(^1\)

Leaf and root

Anticoagulant/antiplatelet drugs\(^17\)

Aspirin\(^18\)

Diuretics\(^10\)

Monoamine oxidase inhibitors (MAOIs)\(^11\)
Seed

Diuretics\textsuperscript{10}

Monoamine oxidase inhibitors (MAOIs)\textsuperscript{11}

**PARTS USED\textsuperscript{1}**

Leaf, root and seed

**REFERENCES**


10. Robbers JE, Tyler VE. Tyler's Herbs of Choice: The Therapeutic Use of


12. The Review of Natural Products by Facts and Comparisons. St. Louis, MO: Wolters


14. Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs

15. Foster S, Tyler VE. Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and


17. Brinker F. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical

18. Eberhard P, Gall HM, Muller I, Moller R. Dramatic augmentation of a food allergy by
PASSION FLOWER

Passiflora incarnata

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Apricot vine, corona de cristo, fleischfarbige, fleur de la passion, flor de passion, madre selva, maracuja, maypop, maypop passion flower, passiflora, Passiflorae herba, passiflore, passiflorina, passionflower, passion vine, passionaria, passionblume, passionflower herb, passionsblumenkraut, purple passion flower, water lemon, wild passion flower

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety associated with adjustment disorders (with hawthorn, black horehound, valerian, cola nut and guarana)</td>
<td>B1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>B2</td>
</tr>
<tr>
<td>Opiate withdrawal (with clonidine)</td>
<td>B2</td>
</tr>
<tr>
<td>Increases exercise capacity in congestive heart failure (with hawthorn)</td>
<td>B2</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotoxic constituents</td>
<td>3</td>
</tr>
<tr>
<td>Mutagenic constituents</td>
<td>3</td>
</tr>
</tbody>
</table>

Both harman and harmine, constituents of passion flower, increased aberrant cell frequency and induced DNA damage in vitro using single-cell gel assay. The authors reported that harman
and harmine are genotoxic and mutagenic\textsuperscript{11}. Harmine was found to be more cytotoxic than harman\textsuperscript{11}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td><strong>Uterine stimulant\textsuperscript{12}</strong></td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that passion flower was a uterine stimulant\textsuperscript{12}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td><strong>Genotoxic constituents\textsuperscript{11}</strong></td>
</tr>
<tr>
<td><strong>Mutagenic constituents\textsuperscript{11}</strong></td>
</tr>
</tbody>
</table>

Both harman and harmine, constituents of passion flower, increased aberrant cell frequency and induced DNA damage in vitro using single-cell gel assay\textsuperscript{11}. The authors reported that harman and harmine are genotoxic and mutagenic\textsuperscript{11}. Harmine was found to be more cytotoxic than harman\textsuperscript{11}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td><strong>Unknown</strong></td>
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</tbody>
</table>

There are no reports in the evidence-based scientific literature of passion flower being either safe or contraindicated during lactation.

**CONSTITUENTS**

Flavonoids\textsuperscript{1}: apigenin, luteolin, quercetin, kaempferol, vitexin

Beta-carboline alkaloids\textsuperscript{5,6}: harmine, harmaline, harmalol, harman, harmin

Cyanogenic glycoside\textsuperscript{5,13,14}: gynocardine
TOXICITY

LD\textsubscript{50} of the closely related species \textit{Passiflora alata} was 456 mg/kg\textsuperscript{15}.

PHARMACOLOGY

Passion flower has been shown to have sedative, hypnotic, anxiolytic, anodyne and antispasmodic effects\textsuperscript{1, 5, 6, 16}.

The alkaloid constituents have central nervous system stimulant activity via a monoamine oxidase mechanism\textsuperscript{16, 17}.

The constituent apigenin binds to central benzodiazepine receptors, thereby causing anxiolytic effects without impairing memory or motor skills\textsuperscript{18}.

Passion flower may reduce amphetamine-induced hypermotility, aggressiveness, and restlessness, and may raise the pain threshold\textsuperscript{13, 16, 19}.

Passion flower may have antibacterial and antifungal activity\textsuperscript{16}.

The constituents harman and harmine are genotoxic and mutagenic, where harmine was found to be more cytotoxic than harman\textsuperscript{11}.

DRUG INTERACTIONS\textsuperscript{1}

Barbiturates\textsuperscript{19}

CNS depressants\textsuperscript{14}

Monoamine oxidase inhibitors (MAOIs)\textsuperscript{16}

PARTS USED

Above ground parts\textsuperscript{1}

REFERENCES


PENNYROYAL

_Hedeoma pulegioides, Mentha pulegium_

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

American pennyroyal, European pennyroyal, lurk-in-the-ditch, mosquito plant, penny royal, pilioleral, pudding grass, pulegium, run-by-the-ground, squaw balm, squawmint, stinking balm, tickweed

INDICATIONS

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient</td>
<td>E</td>
</tr>
<tr>
<td>Emmenagogue</td>
<td>E</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient</td>
<td>2</td>
</tr>
</tbody>
</table>

Pennyroyal has a long tradition of use as an abortifacient. In a 1904 case report, a woman ingested one-half ounce of pennyroyal oil and expelled a dead fetus four days later. In a 1955 case report, a three month pregnant woman ingested two bottles of an unknown amount of pennyroyal with the intention of inducing an abortion; several hours later, the fetus was aborted. A review article on the potential value of plants as sources of anti-fertility agents also reported that pennyroyal was an abortifacient.

In 2 case reports from 1961 and 1985, however, 2 pregnant women consumed pennyroyal in combination with other herbs and this did not lead to an abortion. One women experienced a severe psychotic episode and seizures, while the newborn of the other women was born with mild hyperbilirubinemia.
In a 1996 case report, 24-year-old woman drank glasses of pennyroyal tea with the intention of inducing menstruation\textsuperscript{5}. After repeated intake of pennyroyal tea, the women experienced nausea, severe abdominal cramping for four days and eventually menses began\textsuperscript{5}. In a 1983 case report, a 20-year-old woman took pennyroyal leaves and oil to induce menstruation\textsuperscript{10}. The woman experienced some menstrual spotting from taking pennyroyal leaves and within hours of taking the oil, she was euphoric, vomited and lost consciousness\textsuperscript{10}. The woman was admitted to the hospital, received supportive treatment and recovered fully\textsuperscript{10}. A review article on the potential value of plants as sources of anti-fertility agents also reported that pennyroyal was an emmenagogue\textsuperscript{6}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Emmenagogue\textsuperscript{5, 6, 10}</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hepatotoxicity\textsuperscript{5, 11}</td>
<td>2</td>
</tr>
<tr>
<td>Neurotoxicity\textsuperscript{12}</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotoxic\textsuperscript{5}</td>
<td>2</td>
</tr>
<tr>
<td>Pneumotoxic\textsuperscript{5}</td>
<td>2</td>
</tr>
</tbody>
</table>

Human and animal case reports found that pennyroyal use reduced liver glutathione levels and is hepatotoxic\textsuperscript{5, 11-13}. Neurologic injury developed in two infants after ingestion of pennyroyal tea\textsuperscript{12}. A human case report also found that pennyroyal use may injure the kidneys and the lungs\textsuperscript{5}. 
Carachipita

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortifacient⁴</td>
<td>2</td>
</tr>
<tr>
<td>Multi-system organ failure⁴</td>
<td>2</td>
</tr>
<tr>
<td>Death⁴</td>
<td>2</td>
</tr>
</tbody>
</table>

The South American over-the-counter product called Carachipita, which contains pennyroyal, yerba de la perditz (*Margericarpus pinnatus*), oregano (*Origanum vulgare*) and guaycuri (*Statice brasiliensis*) was found to induce abortion, multi-system organ failure and in one case, death of the mother⁴.

**LACTATION**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity⁵,¹¹</td>
<td>2</td>
</tr>
<tr>
<td>Neurotoxicity¹²</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotoxic⁵</td>
<td>2</td>
</tr>
<tr>
<td>Pneumotoxic⁵</td>
<td>2</td>
</tr>
</tbody>
</table>

Human and animal case reports have documented liver, nerve, kidney and lung toxicity associated with the use of pennyroyal⁵,¹¹,¹². It is unclear if the toxic constituents of pennyroyal cross into breast milk.
Carachipita

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-system organ failure</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
</tr>
</tbody>
</table>

The South American over-the-counter product called Carachipita, which contains pennyroyal, yerba de la perdiz (*Margiricarpus pinnatus*), oregano (*Origanum vulgare*) and guaycuri (*Statice brasiliensis*) was found to induce multi-system organ failure and in one case, death of the mother.

**CONSTITUENTS**

Volatile oils\(^4\): hedeomol, pulegone, alpha-pinene, beta-pinene, limonene, 3-octanone, p-cymene, 3-octylacetate, 3-octanol, 1-octen-3-ol, 3-methylcyclohexanone, menthone, piperitenone

Tannins\(^4\)

Paraffins\(^4\)

**CONTRAINDICATIONS**

Pregnancy\(^2,3\)

Lactation\(^5,11,12\)

Pre-existing kidney, liver, nerve or lung disease\(^5,15\)

Children\(^12\)

**CAUTION**

Alcoholism\(^16\)

Acetominophen use\(^16\)
TOXICITY

Essential oil

LD$_{50}$ in rats (oral)$^{16,17}$: 0.4g/kg

LD$_{50}$ in rabbits (dermal)$^{17}$: 4.2g/kg

Pulegone

LD$_{50}$ in rats (oral)$^{18}$: 0.47g/kg

LD$_{50}$ in rabbits (dermal)$^{18}$: 3.09g/kg

PHARMACOLOGY

The volatile oil pulegone and its metabolites, menthofuran and methofuran's metabolites, may cause hepatotoxicity, neurotoxicity, and bronchiolar epithelial cell destruction$^{5,13,19}$.

Metabolites of pulgegone deplete hepatic glutathione levels$^{5,12,13}$. This leads to metabolite accumulation and direct cellular damage similar to acetaminophen toxicity$^{12}$.

Pulgegone is isomerized to isopulegone, which can be toxic to the lungs and liver$^{20}$.

Excretion of the essential oil irritates the kidneys and the bladder, and reflexively excites uterine contractions$^{16}$.

DRUG INTERACTIONS$^{14}$

Acetominophen$^{21,22}$

Antihistamines$^{23}$

Drugs metabolized by cytochrome P450 enzymes$^{13,24-27}$

Oral hypoglycemic drugs$^{12}$

Hepatotoxic drugs$^{12,15,28}$
PARTS USED\textsuperscript{16}

Aerial parts, oil

REFERENCES


PEPPERMINT

Mentha piperita

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Brandy mint, lamb mint, Menthae piperitae folium, Menthae piperitae Aetheroleum, menthe poivree

INDICATIONS

Oil

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia (with caraway oil)(^2\text{-}^4)</td>
<td>B1</td>
</tr>
<tr>
<td>Tension headaches(^5\text{-}^6)</td>
<td>B1</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome(^7\text{-}^10)</td>
<td>B2</td>
</tr>
<tr>
<td>Post-operative nausea(^11)</td>
<td>B2</td>
</tr>
<tr>
<td>Dyspepsia (with bitter candy tuft, chamomile flower, lemon balm, caraway fruit, licorice root, angelica root, celandine herbs and milk thistle fruit)(^12)</td>
<td>B2</td>
</tr>
<tr>
<td>Common cold (with juniper oil, cajeput oil, eucalyptus oil and methylquinolinium oil)(^13)</td>
<td>C</td>
</tr>
<tr>
<td>Barium enema-related colonic spasm(^14\text{-}^16)</td>
<td>C</td>
</tr>
</tbody>
</table>
### PREGNANCY

<table>
<thead>
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<th>Level</th>
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<tbody>
<tr>
<td>1c</td>
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<table>
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<td>4</td>
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A qualitative study of self-care in pregnancy, birth and lactation was conducted on 27 women in British Columbia (Canada) where 20 women (74%) experienced pregnancy-induced nausea. The authors reported that peppermint was one of the remedies used to treat nausea, but that there was no information on safety during pregnancy.

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>4</td>
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</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents also reported that peppermint was an emmenagogue.

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>4</td>
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</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that peppermint had antigenadotrophic activity in rats.
Food

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Safe(^1)</td>
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<tr>
<td>4</td>
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</tbody>
</table>

Peppermint leaves and oil are believed to be safe during pregnancy if consumed in food amounts\(^1\).

LACTATION

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
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</tbody>
</table>

There are no reports in the evidence-based medical literature of peppermint being either safe or contraindicated during lactation.

Food

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe(^1)</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Peppermint leaves and oil are believed to be safe during lactation if consumed in food amounts\(^1\).

CAUTION

Large amounts of peppermint oil may cause interstitial nephritis and acute renal failure\(^{20}\)

CONSTITUENTS\(^{21}\)

Essential oil\(^{20-24}\): cineol, isomenthone, liminene, menthofuran, menthol, menthone, menthyl acetate, terpenoids

Leaf\(^{21-23}\): caffeic acid, chlorogenic acid, luteolin, hesperidin, rutin, volatile oil, flavonoids, azulene
TOXICITY

Acute oral LD$_{50}$ of menthol$^{25}$: 3.3 g/kg.

Oral administration of a spray-dried infusion of peppermint (4 g/kg) did not result in any macroscopic signs of toxicity or death in mice over a 7-day period$^{26}$.

PHARMACOLOGY

Leaf

Peppermint leaf has antispasmodic, antiflatulent and bile stimulation activity$^{22,27}$.

Oil

The constituent menthol has direct antispasmodic activity on the smooth muscle of the digestive tract through calcium antagonist activity$^{20,28,29}$.

Peppermint oil increases salivation, which increases the swallowing reflex and suppresses the cough reflex$^{20,30}$.

Peppermint oil reduces bronchial secretions and has nasal decongestant activity$^{28}$.

Peppermint oil decreases gas and flatulence by relaxing the lower esophageal sphincter, thereby equalizing the intraluminal pressures between the stomach and esophagus$^{24,31}$.

Peppermint oil has antimicrobial and antiviral activity in vitro$^{23}$.

Peppermint oil may inhibit cytochrome P4503A4$^{32}$.

The volatile oil azulene has anti-inflammatory and anti-ulcer activity$^{23}$.

Topically, peppermint oil is a counterirritant$^{24}$.

DRUG INTERACTIONS

Leaf

Felodipine$^{21}$.
Simvastatin
Cyclosporine
5-fluorouracil

Drugs metabolized by cytochrome P4503A4

Oil

Antacids
Cyclosporine

Drugs metabolized by cytochrome P4503A4

H2-Blockers
Proton pump inhibitors

PARTS USED

Leaf, oil

REFERENCES


**RASPBERRY**

*Rubus idaeus*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**

Red raspberry, *Rubi idaei folium*, rubus, framboise

**INDICATIONS**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour$^{2,3}$</td>
</tr>
</tbody>
</table>

**PREGNANCY**

Leaf

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Risk$^{2,3}$</td>
</tr>
<tr>
<td>Shortens labour and reduces complications$^{2,3}$</td>
</tr>
<tr>
<td>May decrease pre- and post-term births$^{2}$</td>
</tr>
<tr>
<td>Less likely to receive an artificial rupture of the membranes or require a caesarean section, forceps or vacuum birth$^{2}$</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 192 low-risk nulliparous women was conducted where one group consumed raspberry leaf tablets (2 x 1.2 g per day) from 32 weeks' gestation until labor and the other group received a placebo$^{3}$. Raspberry leaf was found to cause no adverse effects for mother or baby$^{3}$. Their findings showed that raspberry leaf did not shorten the first stage of labor, but did shorten the second stage of labor and resulted in a lower rate of forceps deliveries$^{3}$.

A retrospective cohort study of mothers who consumed raspberry leaf products during their pregnancy versus a control group found that raspberry leaf products shortened labour with no
identified side effects for the women or their babies\(^2\). The findings suggested that ingestion of raspberry products might decrease the likelihood of pre- and post-term gestation\(^2\). The findings also suggested that women who ingest raspberry leaf might be less likely to receive an artificial rupture of their membranes, or require a caesarean section, forceps or vacuum birth than the women in the control group\(^2\).

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induces labour(^4)</td>
</tr>
</tbody>
</table>

A survey of midwives in the United States found that 63% of midwives use raspberry leaf to induce labour\(^4\). Raspberry leaf is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to raspberry leaf, mother’s cordial may contain: squaw vine (*Mitchella ripens*), black cohosh (*Cimicifuga racemosa*), blue cohosh (*Caulophyllum thalictroides*) and false unicorn (*Chamaelirium luteum*).

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Uterine stimulant(^5)</td>
</tr>
<tr>
<td>Estrogenic(^1)</td>
</tr>
</tbody>
</table>

A herb toxicology and drug interaction compendium reported that raspberry leaves have uterine stimulant properties\(^5\). A database of herbs and supplements reported that raspberry leaves may have estrogenic properties\(^1\). Raspberry was not reported in the evidence-based literature as having estrogenic properties.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Antigonadotrophic effects(^6)</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that raspberry had antigonadotrophic effects *in vitro*\(^6\).
Fruit

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
</tr>
</tbody>
</table>

Raspberry fruit is not believed to pose a risk to the mother or the baby during pregnancy.

**LACTATION**

Leaves

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Raspberry leaves are not reported in the evidence-based literature as being safe or contraindicated during lactation.

Fruit

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
</tr>
</tbody>
</table>

Raspberry fruit is not believed to pose a risk to the baby during lactation.

**CONSTITUENTS**

Leaf

Tannins

Fruit

Anthocyanins

Phenolic compounds: ellagitannins, ellagic acid

Vitamin C
PHARMACOLOGY

Leaf

Raspberry leaf may decrease contraction of tonic tissues and increase contraction of relaxed tissues\(^4,11\).

In animals, raspberry leaf extract was shown to relax smooth muscle\(^12\).

Fruit

Raspberry fruit is an antioxidant\(^9\).

Extracts of raspberry fruit were found to significantly inhibit mutagenesis on cervical and breast cancer cell lines by both direct-acting and metabolically activated carcinogens\(^13\).

Raspberry cordial and juice were found to have antibacterial activity \textit{in vitro}\(^14\).

DRUG INTERACTIONS

Metformin\(^1\)

PARTS USED\(^5\)

Leaves

References


RED CLOVER

*Trifolium pratense*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Beebread, clovone, cow clover, daidzein, genistein, isoflavone, isoflavones, meadow clover, phytoestrogen, phytoestrogens, purple clover, trefoil, trifolium, wild clover

INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic mastalgia</td>
<td>B2</td>
</tr>
<tr>
<td>Arterial compliance in menopause</td>
<td>B2</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>C</td>
</tr>
<tr>
<td>Menopausal symptoms</td>
<td>D</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>D</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>D</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>D</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause infertility</td>
<td>3</td>
</tr>
</tbody>
</table>

From 1982-1983, serious fertility disturbances were observed in a herd of cattle. The researchers determined that the cause was estrogenic stimulation from eating silage prepared almost entirely from pure red clover aftergrowth. When feeding with the red clover silage was subsequently discontinued, the disturbances ceased to occur and the cows became pregnant more easily.
<table>
<thead>
<tr>
<th>Level</th>
<th>Estrogenic activity&lt;sup&gt;14,15&lt;/sup&gt;</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>Anti-estrogenic activity&lt;sup&gt;16-23&lt;/sup&gt;</td>
<td>3</td>
</tr>
</tbody>
</table>

In human breast cancer cells, red clover was shown to bind to intracellular estrogen receptors and to enhance estrogenic effects<sup>14</sup>. A review article on the potential value of plants as sources of anti-fertility agents reported that red clover has estrogenic activity<sup>15</sup>.

In addition to having estrogenic activity, red clover was reported to have anti-estrogenic properties<sup>16-23</sup>.

| Level | Increases progesterone synthesis<sup>24</sup> | 3 |

The red clover constituent biochanin A was found to increase progesterone synthesis by 40-50% in bovine granulosa cells<sup>24</sup>.

| Level | Crosses the placenta<sup>25</sup> | 3 |

In a study of human amniotic fluid following phytoestrogen ingestion, dietary phytoestrogens were found in 96.2% of second trimester amniotic fluid samples tested<sup>25</sup>. The second trimester amniotic fluid contained quantifiable levels of formononetin, biochanin A and coumestrol, all constituents of red clover<sup>25</sup>.

| Level | Potential abortifacient<sup>12</sup> | 4 |

An evidence-based herbal monograph database reported that red clover has been implicated as a cause of abortion in grazing livestock<sup>12</sup>.
Food amounts

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Red clover was reported to be of minimal risk when consumed in food amounts<sup>26</sup>.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Estrogenic activity&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Increases progesterone synthesis&lt;sup&gt;24&lt;/sup&gt;</td>
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In human breast cancer cells, red clover was shown to bind to intracellular estrogen receptors and to enhance estrogenic effects<sup>14</sup>. The red clover constituent biochanin A was found to increase progesterone synthesis by 40-50% in bovine granulosa cells<sup>24</sup>.

Food amounts

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<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Red clover was reported to be of minimal risk when consumed in food amounts<sup>26</sup>.

**CONSTITUENTS**

Isoflavones<sup>1</sup>: biochanin A, formononetin, coumestrol

**TOXICITY**

Insufficient human data available<sup>12</sup>

In grazing animals, red clover ingestion has been associated with cachexia, bloating, infertility, growth disorders and abortion<sup>12, 27</sup>
PHARMACOLOGY

The phytoestrogens biochanin A and formononetin, and other isoflavones are metabolized to the isoflavones genistein and daidzein, respectively, when ingested.\textsuperscript{16, 28, 29}

Red clover has estrogenic and anti-estrogenic properties.\textsuperscript{16-23}

Isoflavones have a higher affinity for beta estrogen receptors (heart, vasculature, bone and bladder) than alpha estrogen receptors\textsuperscript{16, 18, 30-33}.

Red clover may prevent osteoporosis due to its weak estrogenic activity and to the osteoclast inhibitory activity of its metabolite genistein\textsuperscript{16, 18, 32, 34}.

Red clovers improves systemic arterial compliance, thereby preventing cardiovascular disease\textsuperscript{3, 28, 32}.

Red clover increases bile acid excretion and up-regulates low-density lipoprotein (LDL) receptors\textsuperscript{18, 35, 36}.

Red clover may have anticarcinogenic activity, particularly in reducing the risk of endometrial cancer, due to estrogenic and anti-estrogenic activity\textsuperscript{37-40}.

Red clover may have anti-coagulant effects\textsuperscript{41}.

Red clover may interfere with the cytochrome P450 CYP3A4 enzyme\textsuperscript{42, 43}.

**DRUG INTERACTIONS\textsuperscript{1}**

Anticoagulant/antiplatelet drugs\textsuperscript{43}

Estrogen or oral contraceptives\textsuperscript{43-45}

Tomoxifen\textsuperscript{17}

Drugs metabolized by cytochrome P450 CYP3A4\textsuperscript{42, 43}

**PARTS USED\textsuperscript{1}**

Flower top
REFERENCES


29. Setchell KD. Absorption and metabolism of soy isoflavones-from food to dietary supplements and adults to infants. J Nutr 2000; 130:654S-5S.


RYE ERGOT

*Claviceps purpurea*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Cockspur rye, hornseed, mother of rye, *Secale cornutum*, smut rye, spurred rye

INDICATIONS

Oxytoxin-ergot preparations

<table>
<thead>
<tr>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Prevention of post-partum hemorrhage</td>
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</table>

Ergot derivatives

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia and age-related cognitive impairment</td>
</tr>
<tr>
<td>Migraine headaches</td>
</tr>
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</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Potentially teratogenic</td>
</tr>
</tbody>
</table>

A literature review on ergot and ergotamine reported that ergotamine is a suspected teratogen, where clinical reports in humans have been anecdotal, but in many the malformations are consistent with vascular injury. The author reported that although epidemiologic studies have not shown any clear increase in malformations among exposed infants, this may reflect the limited exposure and toxicity when used episodically. The author recommended that ergotamine be avoided in pregnancy.
May cause convulsive ergotism

A historical review was conducted on the epidemics of "convulsive ergotism" between 1085 and 1927 of the Rhine Valley in Europe. The clinical features of convulsive ergotism are muscle twitches, changes in mental state, hallucinations, sweating, and fever lasting for several weeks. The author suggested that these symptoms represented a serotonegic overstimulation of the central nervous system, i.e., the serotonin syndrome.

A herbal contraindication and drug interaction compendium reported that rye ergot is an emmenagogue, uterine stimulant, abortifacient and has oxytotic properties.

Cabergoline (Ergot derivative)

A follow-up study on 204 live-births in order to assess the reproductive safety of cabergoline, an ergot derivative, showed no increase in miscarriage rate, a distribution of birthweights and sex ratio within the expected range, and no increased rate of congenital malformations. A further follow-up of babies, limited to 107 cases, indicated normal physical and mental development.
<table>
<thead>
<tr>
<th>Level</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Non-teratogenic\textsuperscript{11}</td>
<td>3</td>
</tr>
<tr>
<td>Does not impair fertility in males\textsuperscript{11}</td>
<td>3</td>
</tr>
<tr>
<td>Non-toxic to neonates\textsuperscript{11}</td>
<td>3</td>
</tr>
</tbody>
</table>

A study on the teratogenicity of cabergoline in animals concluded that cabergoline did not impair fertility in the male rat, was not teratogenic in mice and rabbits, did not affect the latter phase of gestation or parturition in the rat, and was not toxic when administered directly to neonatal rats\textsuperscript{11}.

\textit{Claviceps purpurea} grown on wheat

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Reproductive problems\textsuperscript{12}</td>
<td>3</td>
</tr>
</tbody>
</table>

Ergot alkaloids from \textit{Claviceps purpurea} grown on wheat can cause reproductive problems in pigs\textsuperscript{12}.

**LACTATION**

Ergot derivatives

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit lactation\textsuperscript{13, 14}</td>
<td>1a</td>
</tr>
</tbody>
</table>

A number of randomized clinical trials reported that ergot derivatives inhibit post-partum lactation\textsuperscript{13, 14}.
*Claviceps purpurea* grown on wheat

<table>
<thead>
<tr>
<th>Level</th>
<th>Lactational failure&lt;sup&gt;12&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
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</tbody>
</table>

Ergot alkaloids from *Claviceps purpurea* grown on wheat are associated with lactational failure in pigs<sup>12</sup>.

**CONTRAINDICATIONS**<sup>9</sup>

Peripheral blood flow disorders

Coronary insufficiency

Slow GI absorption

Pre-existing vascular pathology

Hypertonia

Liver disease

Infection

Fever

**TOXICITY**

Toxic dose of rye ergot extract<sup>9</sup>: 1.0-3.9g

Lethal dose of rye ergot alkaloids<sup>9</sup>: 1g (adults) and 12mg (infants)

Lethal dose of ergotamine tartrate<sup>9</sup>: 26 mg (oral) and 0.5-1.5mg (IM)

LD<sub>50</sub> of the rye ergot alkaloid elymoclavine<sup>15</sup>: 350 mg/kg (mice) and 145 mg/kg (rats)
CONSTITUENTS

Indole alkaloids<sup>9</sup>: ergonovine, ergocornine, ergotamine, ergocryptine, ergosine, ergocristine

PHARMACOLOGY

Through alpha-adrenergic blocking and antagonism of 5-hydroxytryptamine, rye ergot stimulates smooth muscles and post-ganglionic synapses of the sympathetic nerves to the uterus, bladder, heart, blood vessels and iris<sup>9</sup>.

Ergot alkaloids produce vasoconstriction and myometrial stimulation<sup>16</sup>.

The ergot alkaloids and derivatives have central, neurohumoral and peripheral effects<sup>1</sup>.

The ergot alkaloids and derivatives bind to noradrenaline, serotonin, or dopamine receptors<sup>17</sup>.

The ergot alkaloids are serotonin agonists<sup>9</sup>. Dihydroergotamine binds to serotonin receptors in the dorsal horn of the spinal cord, which is the site of neuropathological changes in convulsive ergotism<sup>8</sup>.

DRUG INTERACTIONS

Ergot Alkaloids<sup>1</sup>

Sympathomimetics<sup>16</sup>

PARTS USED

Dried sclerotium grown on <em>Secale</em> (rye) kernels<sup>9</sup>

REFERENCES


SENNA

*Cassia acutifolia, C. angustifolia, C. senna, C. lanceolata*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Alexandrian senna, alexandrinische senna, casse, Indian senna, khartoum senna, sena alejandrina, séné d'Egypte, Sennae folium, Sennae fructus, Sennae fructus acutifoliae, Sennae fructus angustifolia, tinnevelly senna, true senna

INDICATIONS

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation²⁻⁴</td>
</tr>
<tr>
<td>B1</td>
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</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk⁵</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Does not stimulate uterine motility⁵</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

A study was conducted to evaluate the effects of sennosides on uterine motility in the pregnant ewe⁵. The experiments showed that sennosides did not stimulate uterine motility in the pregnant ewe, but slightly depressed it in some ewes⁵. Cervix motility was never influenced and pregnancy maintenance was normal in all ewes⁵.

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Minimal risk⁶</td>
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<tr>
<td>4</td>
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</tbody>
</table>

A review article reported that senna would appear to be the stimulant laxative of choice during pregnancy⁶.
<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Potential abortifacient&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emmenagogue&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A toxicology and drug interaction compendium reported that senna is an emmenagogue and potential abortifacient<sup>7</sup>. There are no reports in the evidence-based medicine literature of senna being an emmenagogue or potential abortifacient.

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Conflicting evidence</td>
</tr>
<tr>
<td>Non-genotoxic&lt;sup&gt;8,9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Genotoxic&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A toxicology and drug interaction compendium reported that senna is genotoxic due to its aloe-emodin content<sup>7</sup>. A review study on the potential genotoxic and mutagenic properties of senna reported that human clinical trials and animal data do not support concerns that senna laxatives pose a genotoxic risk to humans when consumed under prescribed use conditions<sup>8,9</sup>.

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>Avoid during pregnancy&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A compendium on herbal safety reported that senna should be avoided during pregnancy<sup>10</sup>. There are no reports in the evidence-based medicine literature of senna being contraindicated during pregnancy.
LACTATION

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Minimal risk$^{4,11}$</td>
</tr>
<tr>
<td>4</td>
<td>Safe according to the American Association of Pediatrics (AAP)$^{11}$</td>
</tr>
</tbody>
</table>

A clinical trial was conducted on the effectiveness of senna in the immediate postpartum period in white and black patients with matching placebo$^4$. The author reported that it was well tolerated with minor abdominal cramps occurring in 13% of the patients treated with standardized senna$^4$. The author reported that there was no evidence to suggest that standardized senna had any effect whatsoever on a breast-fed baby if taken by the mother$^4$.

Senna is considered compatible by the American Association of Pediatrics (AAP) for breastfeeding$^{11}$.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low levels excreted in breast milk$^{12,13}$</td>
</tr>
</tbody>
</table>

A study was conducted on the excretion of rhein, a cathartic metabolite from sennosides, in breast milk samples of 15 post-partum women for at least 24 h after the intake of a therapeutic dose (15 mg sennosides/day) of senna$^{12}$. The authors observed that the amount of rhein transmitted to the infant was 0.3% of the rhein intake of the mother, which is far below the oral rhein dose necessary for inducing a laxative effect$^{12}$. The authors also reported that none of the breast-fed infants showed any difference in stool consistency in comparison with the non breast-fed infants$^{12}$. Another study in 100 breast milk samples found similar results$^{13}$.

CONTRAINDICATION$^7$

Intestinal obstruction

Abdominal pain of unknown origin
Intestinal inflammation

Prolapsed rectum or anus

Kidney dysfunction

Children under twelve

CAUTION

Avoid use for longer than one to two weeks as frequent use causes the colon to function poorly, creating laxative dependence\textsuperscript{10}.

Constituents

Anthraquinones\textsuperscript{14,15}: sennosides A and B (mostly), sennosides C and D (minor amounts)

TOXICITY

LD\textsubscript{50} (intraperitoneal)\textsuperscript{16}: 500-750 mg/kg

PHARMACOLOGY

Senna leaf and fruit are stimulant laxatives, where the leaf is a stronger cathartic than the fruit\textsuperscript{17,18}.

The cathartic action is limited primarily to the colon\textsuperscript{17}.

Sennosides irritate the lining of the large intestine, causing contraction\textsuperscript{1}.

Sennosides A and B appear to induce fluid secretion in the colon\textsuperscript{1}.

Prostaglandins may be involved in the laxative effect\textsuperscript{14}.

Anthroquinones produce a laxative effect 8-12 hours after administration, though sometimes up to 24 hours can be required\textsuperscript{19}.

Anthroquinone laxative use is not associated with an increased risk of developing colorectal adenoma or carcinoma\textsuperscript{20}.
DRUG INTERACTIONS

Cardiac glycoside drugs

PARTS USED

Leaf, fruit

REFERENCES


**SIBERIAN GINSENG**

*Eleutherococcus senticosus*

**SYNONYMS/COMMON NAMES/RELATED SUBSTANCES**

Ci wu jia, ciwujia, devil's bush, devil's shrub, eleuthera, eleuthero, eleuthero ginseng, eleuthrococ, eleuthrococ, *Eleutherococci radix*, eleuthrococcus, ginseng, phytoestrogen, prickly eleuthrococ, , russian root, shigoka, thorny bearer of free berries, touch-me-not, untouchable, ussuri, ussurian thorny pepperbrush, wild pepper, wu jia pi, wu-jia.

**INDICATIONS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular late potential (coronary artery disease and myocarditis)</td>
<td>B1</td>
</tr>
<tr>
<td>Acute cerebral infarction</td>
<td>B2</td>
</tr>
<tr>
<td>Hyperlipidemia (with <em>Elscholtzia splendens</em>)</td>
<td>C</td>
</tr>
<tr>
<td>Cognitive performance</td>
<td>C</td>
</tr>
<tr>
<td>Herpes Simplex type II</td>
<td>C</td>
</tr>
<tr>
<td>Adaptogen</td>
<td>F</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence to support androgenization</td>
<td>2</td>
</tr>
</tbody>
</table>

A case was reported of a 30-year-old woman who gave birth to a full-term baby boy with signs of androgenization following ingestion of “ginseng” during the woman’s pregnancy. After
further investigation, the herbal preparation used by the mother appeared to be adultered by the herb silk vine \((\text{Periploca sepium})\) and not Siberian ginseng \((\text{Eleutherococcus senticosus})^{8}\)

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk(^{10})</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevents embryotoxic effects(^{10})</td>
<td>3</td>
</tr>
</tbody>
</table>

Administration of Siberian ginseng extract during prenatal and pre-embryonic periods of development prevented embryotoxic effects in pregnant rats treated with ethanol and sodium salicylate\(^{10}\).

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk(^{11})</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticarcinogenic effects(^{11})</td>
<td>3</td>
</tr>
</tbody>
</table>

Administration of Siberian ginseng inhibited the carcinogenesis induced by transplacental administration of N-nitrosoethylurea in rats\(^{11}\). This lead to longer survival of the rats and lower occurrence and/or multiplicity of tumors (mainly those of the central nervous system)\(^{11}\).

| Level | Unknown | 5 |

There are no reports in the evidence-based literature of Siberian ginseng being either safe or contraindicated during pregnancy.

**LACTATION**

| Level | Unknown | 5 |

There are no reports in the evidence-based literature of Siberian ginseng being either safe or contraindicated during lactation.
CONSTITUENTS

Eleutherosides A through M\textsuperscript{12}

Saponins\textsuperscript{1}: daucosterol, beta-sitosterol, hederasaponin B

Coumarins\textsuperscript{1}: isofraxidin

Lignans\textsuperscript{1}: sesamin, syringaresinol

Phenylpropanoids\textsuperscript{1}: syringin, caffeic acid, sinapyl alcohol, coniferyl aldehyde, protocatechuic acid

Betulinic acid\textsuperscript{1}

Vitamin E\textsuperscript{1}

TOXICITY

LD\textsubscript{50} of root: 31 g/kg\textsuperscript{13}

LD\textsubscript{50} of liquid extract: 10 ml/kg\textsuperscript{14}

PHARMACOLOGY

Siberian ginseng inhibits the alarm-reaction to stress and decreases the activation of the adrenal cortex\textsuperscript{15}.

Siberian ginseng has anti-viral activity, where it inhibits human rhinovirus, respiratory syncytial virus (RSV), and influenza A virus\textsuperscript{16}.

Siberian ginseng increases lymphocyte count, particularly T-lymphocytes, and increases phagocyte activity\textsuperscript{12,17,18}.

Several constituents of Siberian ginseng have antioxidant and possible anticancer effects, particularly on leukemia cells\textsuperscript{12,19}.

The constituent coniferyl aldehyde protects DNA against breakage caused by ultraviolet light\textsuperscript{12}. 
The constituent protocatechuic acid may inhibit platelet aggregation\textsuperscript{20}.

Siberian ginseng eleutheroside G and saponins may have hypoglycemic activity\textsuperscript{20-22}.

Siberian ginseng may have anti-tubercular activity\textsuperscript{23}.

Intravenous Siberian ginseng may reduce myocardial infarct size\textsuperscript{24}.

Siberian ginseng may inhibit cytochrome P450 CYP1A2 and CYP2C9 enzymes\textsuperscript{25, 26}. It does not appear to inhibit drug metabolism by CYP2D6 and CYP3A4 enzymes in humans\textsuperscript{25, 27}.

**DRUG INTERACTIONS\textsuperscript{1}**

Alcohol (ethanol)\textsuperscript{26}

Anticoagulant/antiplatelet drugs\textsuperscript{20}

Anti-diabetic drugs\textsuperscript{21}

CNS depressants\textsuperscript{26}

Drugs metabolized by cytochrome P450 1A2 (CYP1A2) and P450 2C9 (CYP2C9) enzymes\textsuperscript{25, 26}

Digoxin (Lanoxin)\textsuperscript{9, 28}

**PARTS USED\textsuperscript{1}**

Root, rhizome

**REFERENCES**


SQUAW VINE

*Mitchella repens*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS\(^1\)

Checkerberry, deerberry, hive vine, noon kie oo nah yeah, one-berry, partridgeberry, running box, squaw berry, squawvine, twinberry, two-eyed berry, winter clover

**INDICATIONS**

<table>
<thead>
<tr>
<th>Induces labour</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
</tr>
</tbody>
</table>

**PREGNANCY**

<table>
<thead>
<tr>
<th>Induces labour</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Squaw vine is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to squaw vine, mother’s cordial typically contains: Black cohosh (*Cimicifuga racemosa*), raspberry (*Rubus idaeus*), blue cohosh (*Caulophyllum thalictroides*) and false unicorn (*Chamaelirium luteum*).

<table>
<thead>
<tr>
<th>Abortifacient(^2)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

A botanical safety compendium reported that squaw vine is a potential abortificaint\(^2\). There are no reports in the evidence-based scientific literature of squaw vine being either safe or contraindicated during pregnancy.
LACTATION

<table>
<thead>
<tr>
<th>Level</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based scientific literature of squaw vine being either safe or contraindicated during lactation.

CONSTITUENTS\(^1,3\)

Resin, wax, mucilages, dextrin, saponins, alkaloids, glycosides, tannins

PHARMACOLOGY

No available information

DRUG INTERACTIONS

None documented

PART USED

Above ground parts\(^1\)

REFERENCES


ST. JOHN’S WORT

Hypericum perforatum

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Amber, amber touch-and-heal, demon chaser, fuga daemonum, goatweed, hardhay, hypereikon, hyperici herba, hypericum, Johns wort, klamath weed, millepertuis, Rosin rose, Saint Johns wort, Saint John's wort, Saynt Johannes wort, SJW, St Johns wort, St John's wort, tipton weed

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate depression</td>
<td>A</td>
</tr>
<tr>
<td>Anxiety (with valerian)</td>
<td>B2</td>
</tr>
<tr>
<td>Acute otitis media (with Verbascum thapsus, Calendula flores and Allium sativum)</td>
<td>B2</td>
</tr>
<tr>
<td>Obsessive compulsive disorder (OCD)</td>
<td>C</td>
</tr>
<tr>
<td>Psychological menopause symptoms</td>
<td>C</td>
</tr>
<tr>
<td>Premenstrual syndrome (PMS)</td>
<td>C</td>
</tr>
<tr>
<td>Chronic colitis (with Taraxacum officinale, Melissa officinalis, Calendula officinalis, Calendula officinalis and Foeniculum vulgare)</td>
<td>C</td>
</tr>
<tr>
<td>Seasonal affective disorder (SAD)</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
<td>2</td>
</tr>
</tbody>
</table>
A case of a 38-year-old women who started taking St. John’s wort at 24 weeks gestation was reported in a letter to the editor\textsuperscript{16}. The woman’s pregnancy was unremarkable, with the exception of late onset of thrombocytopenia (the author did not attribute this to St. John’s wort)\textsuperscript{16}. The offspring was born healthy, had a normal birth weight, normal APGAR scores and physical examination and laboratory results were normal\textsuperscript{16}. Behavioural assessment at 4 and 23 days was within normal\textsuperscript{16}.

<table>
<thead>
<tr>
<th>Minimal risk\textsuperscript{17}</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not affect cognitive development\textsuperscript{17}</td>
<td>3</td>
</tr>
</tbody>
</table>

A study on the cognitive impact of prenatal exposure to St. John’s wort in mice for 2 weeks before mating and throughout gestation found that prenatal exposure to a therapeutic dose of St. John’s wort did not have a major impact on certain cognitive tasks in mice offspring\textsuperscript{17}.

<table>
<thead>
<tr>
<th>Minimal risk\textsuperscript{18}</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower offspring weight\textsuperscript{18}</td>
<td>3</td>
</tr>
</tbody>
</table>

A study was conducted where Sprague-Dawley rats were exposed to dietary doses of St. John’s wort 1-25 times the recommended human dose\textsuperscript{18}. St. John’s wort had no effect on maternal weight gain or duration of gestation\textsuperscript{18}. Offspring body weights were similar to controls, but some treated groups, offspring weighed significantly less than the controls\textsuperscript{18}. There were no S. John’s wort-related behavioral alterations on any measure\textsuperscript{18}. Whole and regional brain weights of offspring at adulthood indicated no significant effects of St. John’s wort\textsuperscript{18}. 
A behavioural study on mice offspring exposed antenatally to the Saint John's wort found that birth weights of male offspring were less in the Saint John's wort group than in the placebo group\(^9\). Offspring in both treatment groups showed no long-term statistical differences in early developmental tasks, locomotor activity, and exploratory behavior throughout development\(^9\). Performances on a depression task and on anxiety tasks revealed no differences between treatment groups\(^9\).

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Minimal risk(^9)</td>
</tr>
<tr>
<td>3</td>
<td>Lower birth weights(^9)</td>
</tr>
<tr>
<td>3</td>
<td>No long-term behavioural deficits(^9)</td>
</tr>
</tbody>
</table>

St. John’s wort was administered to mice in order to determine whether prenatal exposure to the herb affects long-term growth and physical maturation of mouse offspring\(^20\). Maternal administration of St. John’s wort before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring\(^20\).

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Minimal risk(^20)</td>
</tr>
<tr>
<td>3</td>
<td>Does not affect long-term growth and physical maturation(^20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Conflicting evidence</td>
</tr>
<tr>
<td>3</td>
<td>Non-mutagenic(^21)</td>
</tr>
<tr>
<td>3</td>
<td>Teratogenic(^22)</td>
</tr>
</tbody>
</table>
A study on organogenesis found that hypericin induced teratogenic effects in whole rat embryo cultures. A study on mammalian cells, however, showed that a standardized aqueous ethanolic of St. John’s wort did not induce any mutagenic effects.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases uterine tone</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

St. John’s wort was shown to increase uterine tone in animals.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmenagogue</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Uterine stimulant</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Abortifacient</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that St. John’s wort is an abortifacient, emmenagogue and uterine stimulant.

**Homeopathic *Hypericum perforatum* (Hypericum)**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Risk</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

A homeopathic preparation of *Hypericum perforatum*, called Hypericum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Although the principles of homeopathy are difficult to apply to evidence-based medicine research, a systematic review determined that homeopathic preparations do not significantly differ from placebo.
**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause colic, drowsiness or lethargy(^{26})</td>
</tr>
<tr>
<td>Minimal risk(^{26})</td>
</tr>
</tbody>
</table>

A prospective observational cohort study was conducted on 33 breastfeeding women receiving St. John's wort (Group 1) and for comparison, 101 disease-matched (Group 2) and 33 age- and parity-matched non-disease controls (Group 3)\(^{26}\). In the group receiving St. John’s wort, there were 2 cases of colic, 2 cases of drowsiness and 1 case of lethargy\(^{26}\). Specific medical treatment was not required for the infants\(^{26}\). No significant difference was observed in the frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life\(^{26}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses into breast milk(^{27})</td>
</tr>
<tr>
<td>Minimal risk(^{27})</td>
</tr>
</tbody>
</table>

An analysis was performed on four breast-milk samples (fore and hind milk) during an 18-hour period from a mother with post-natal depression who had taken St. John’s wort during pregnancy in order to measure concentration of hypercin and hyperforin\(^{27}\). Only hyperforin was excreted into breast milk at a low level\(^{27}\). No side effects were seen in the mother or infant\(^{27}\).

**Homeopathic Hypericum perforatum** (Hypericum)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Risk(^{25})</td>
</tr>
</tbody>
</table>

A homeopathic preparation of *Hypericum perforatum*, called Hypericum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Although the principles of homeopathy are difficult to apply to evidence-based medicine research, a
systematic review determined that homeopathic preparations do not significantly differ from placebo\textsuperscript{25}.

**CONSTITUENTS**

Naphthodianthrones\textsuperscript{28}: hypericin, pseudohypericin

Flavonoids\textsuperscript{28}: quercetin, quercetrin, amentoflavone, hyperin

Phloroglucinols\textsuperscript{28}: hyperforin, adhyperforin

Essential oil\textsuperscript{28}

**TOXICITY**

Delayed hypersensitivity photodermatitis\textsuperscript{29-31}.

Hypericin is believed to be the photosensitizing agent present in St. John’s wort\textsuperscript{32, 33}.

**PHARMACOLOGY**

St. John's wort effects on serotonin may be primarily responsible for its antidepressant activity\textsuperscript{34}.

Extracts of St. John's wort inhibit the reuptake of serotonin, norepinephrine, and dopamine in vitro\textsuperscript{34-36}.

Hyperforin and adhyperforin were shown to modulate the effects of serotonin, dopamine, and noradrenaline, and to act as serotoninergic 5-HT\textsubscript{3} and 5-HT\textsubscript{4} receptor antagonists\textsuperscript{36-39}.

Hypericin inhibits in vitro almost irreversibly both type A and B monoamine oxidase (MAO) in rat brain mitochondria\textsuperscript{40}.

St. John's wort induces some of the cytochrome P450 (CYP) enzymes and may interfere with drug metabolism\textsuperscript{41}.

Topical application of St John's wort inhibits the proliferation of T lymphocytes in inflammatory skin disorders\textsuperscript{42}.

St. John’s wort has antibacterial activity\textsuperscript{43}.
In human and animal cancer cells, hyperforin inhibited tumour cell growth by induction of apoptosis.44

**DRUG INTERACTIONS**

5-HT1 agonists45, 46

Alprozolam47

Aminolaevulinic acid48

Amitriptyline49-51

Analgesics with serotonergic activity34-36, 46

Antidepressants46, 52-54

Barbituates55

Carbamazepine56

Cyclosporine45, 50, 51, 57-67

Digoxin45, 51, 68-70

Dextromethorphan34-36, 46

Fenfluramine54

Fexofenadine71

Irinotecan72, 73

Monoamine Oxidase Inhibitors (MAOIs)36, 38

Mycophenolate mofetil74

Narcotics55, 75

Nelazodone76
Nonnucleoside Reverse Transcriptase Inhibitors\textsuperscript{50, 77, 78}

Nortriptyline\textsuperscript{49, 51}

Oral contraceptives\textsuperscript{45, 79-81}

Paroxetine\textsuperscript{46, 53, 54}

Phenobarbital\textsuperscript{45}

Phenprocoumon\textsuperscript{45}

Phenytoin\textsuperscript{45}

Photosensitizing drugs\textsuperscript{52}

Protease Inhibitors (PIs)\textsuperscript{45, 51, 77}

Reserpine\textsuperscript{55}

Sertraline\textsuperscript{76}

Simvastatin\textsuperscript{82}

Tacrolimus\textsuperscript{74, 83}

Theophylline\textsuperscript{45, 51, 84}

Warfarin\textsuperscript{45, 79, 85}

Drugs metabolized by cytochrome P450 enzymes\textsuperscript{41, 45, 47, 51, 60, 69, 70, 77, 79, 86}

**PARTS USED**

Whole plant\textsuperscript{87}

**REFERENCES**


**TURMERIC**

*Curcuma longa, Curcuma aromatica*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Curcuma, *Curcuma longae rhizoma*, curcumin, Indian saffron, tumeric, turmeric root

**INDICATIONS**

Oral

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>B1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>B1</td>
</tr>
<tr>
<td>Biliary dyskinesia (with celandine)</td>
<td>B2</td>
</tr>
<tr>
<td>Gallstone prevention (cholagogue)</td>
<td>B2</td>
</tr>
<tr>
<td>Osteoarthritis (with Withania somnifera, Boswellia serrata and a zinc complex)</td>
<td>B2</td>
</tr>
<tr>
<td>HIV</td>
<td>B2</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>C</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>C</td>
</tr>
<tr>
<td>Uveitis</td>
<td>C</td>
</tr>
<tr>
<td>Cancer prevention</td>
<td>D</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>D</td>
</tr>
</tbody>
</table>
Topical

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cancer prevention(^{19})</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scabies(^{20})</td>
<td>D</td>
</tr>
</tbody>
</table>

**PREGNANCY**

Therapeutic doses

<table>
<thead>
<tr>
<th>Level</th>
<th>Non-teratogenic(^{21-23})</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-mutagenic in high doses(^{24,25})</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Non-toxic in high doses(^{24,25})</td>
<td>3</td>
</tr>
</tbody>
</table>

Animal experiments reported that oral turmeric was not teratogenic in mice or rats\(^{21-23}\). Turmeric was reported as non-mutagenic and non-toxic at high doses in rats and monkeys\(^{24,25}\).

| Level  | Inhibits uterine stretching\(^{26}\) | 3 |

An animal experiment of the stretch of the uterus imposed by the growing fetus, which contributes to the onset of labor, showed that curcumin inhibited one of the signalling pathways (c-Jun NH2-terminal kinase (JNK)) necessary for optimal stretching of the uterus\(^{26}\).

| Level  | Minimal risk\(^{27}\) | 4 |

A retrospective explorative study was conducted to ascertain the knowledge, attitudes and practices regarding diet patterns during pregnancy and lactation among Non-Bengali Muslim mothers\(^{27}\). Turmeric was believed to improve the baby's complexion and to protect the baby and
mother from cough and cold\textsuperscript{27}. No adverse effects associated with the ingestion of turmeric during pregnancy were reported\textsuperscript{27}.

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|}
\hline
Potential abortifacient\textsuperscript{28} & 4 \\
\hline
Emmenagogue\textsuperscript{28} & 4 \\
\hline
Uterine stimulant\textsuperscript{28} & 4 \\
\hline
\end{tabular}
\caption{Level of risk for potential adverse effects of turmeric during pregnancy.}
\end{table}

A review article on the potential value of plants as sources of anti-fertility agents reported that turmeric was a potential abortifacient, emmenagogue and uterine stimulant\textsuperscript{28}.

Spice

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|}
\hline
Minimal risk\textsuperscript{1} & 4 \\
\hline
\end{tabular}
\caption{Level of risk for turmeric during pregnancy if used as a spice.}
\end{table}

A natural medicine compendium reported that turmeric is of minimal risk during pregnancy if used as a spice\textsuperscript{1}.

**LACTATION**

Therapeutic doses

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|}
\hline
Crosses into breast milk\textsuperscript{29,30} & 3 \\
\hline
\end{tabular}
\caption{Level of risk for the passage of active constituents and/or metabolites of turmeric and curcumin via the translactational route into breast milk.}
\end{table}

Animal experiments reported the passage of active constituents and/or metabolites of turmeric and curcumin via the translactational route into breast milk\textsuperscript{29,30}. There is no report in the evidence-based literature of turmeric being either safe or contraindicated during lactation.

\begin{table}[h!]
\centering
\begin{tabular}{|l|c|}
\hline
Minimal risk\textsuperscript{27} & 4 \\
\hline
\end{tabular}
\caption{Level of risk for turmeric during lactation.}
\end{table}
A retrospective explorative study was conducted to ascertain the knowledge, attitudes and practices regarding diet patterns during pregnancy and lactation among Non-Bengali Muslim mothers. Turmeric was believed to improve the baby's complexion and to protect the baby and mother from cough and cold. No adverse effects associated with the ingestion of turmeric during lactation were reported.

Spice

<table>
<thead>
<tr>
<th>Minimal risk (^1)</th>
<th>4</th>
</tr>
</thead>
</table>

A natural medicine compendium reported that turmeric is of minimal risk during lactation if used as a spice. \(^1\)

**CONSTITUENTS\(^1,31\)**

Diarylheptanoids: Curcumin

Volatile oils: turmerone, zingiberene, bisabolona, guaiane, cirlone

Sugars: glucose, fructose, arabinose

Vitamin C

**TOXICITY**

LD\(_{50}\) of curcumin in mice (oral)\(^2\): >2g/kg

Turmeric was reported as non-mutagenic and non-toxic at high doses\(^24,25\). 300mg/kg in rats and 2.5g/kg in monkeys

**PHARMACOLOGY**

In clinical trials, curcumin is a potent anti-inflammatory agent where its action is reported to be comparable to phenylbutazone.\(^2\)
In vitro, curcumin was shown to inhibit IL-8, MIP-1alpha, MCP-1, IL-1beta, TNF-alpha, 5-lipoxygenase activity, cyclooxygenase activity and 5-hydroxy-eicosatetraenoic acid (5-HETE) formation, leukotriene formation and platelet aggregation, and to increase the breakdown of fibrin\textsuperscript{32-38}.

Curcumin was shown to significantly decrease the level of serum lipid peroxides (33%), increase HDL cholesterol (29%) and decrease total serum cholesterol, thereby having a preventative effect on arterial disease\textsuperscript{18}.

Turmeric increases bile secretion and bile flow, and induces contraction of the human gall-bladder (cholagogue)\textsuperscript{6,39,40}.

Turmeric has significant anti-oxidant activity and may protect DNA against free radical damage\textsuperscript{17,41,42}.

Turmeric may significantly increase the gastric wall mucus and restore the non-protein sulphydryl (NP-SH) content in the stomachs\textsuperscript{43}.

Curcumin and turmeric were shown to inhibit HIV-1, HIV-2 and HIV-integrase\textsuperscript{44-46}.

Curcumin was shown to have anti-mutagen activity, anti-carcinogen activity, chemopreventive activity in colon carcinogenesis, reduce urinary excretion of mutagens in smokers, and inhibit and/or induce apoptosis in prostate cancer cells, skin and gastric tumors, colonic epithelial cell dysplasia, and others\textsuperscript{12-16}.

Curcumin is a potent inhibitor of cytochrome P450 (CYP) 1A1/1A2, a less potent inhibitor of CYP 2B1/2B2, and a weak inhibitor of CYP 2E1\textsuperscript{47}.

Turmeric may decrease hepatocyte glutathione levels and curcumin appears to induce glutathione-s-transferase activity in mice\textsuperscript{48,49}.

**Drug Interactions**

Antiplatelet Drugs\textsuperscript{50}

Reserpine and Indomethacin\textsuperscript{50}
Drugs metabolized by cytochrome P450 (CYP) 1A1/1A2, CYP 2B1/2B2 and CYP 2E1 enzymes.

PARTS USED

Rhizome

REFERENCES


9. Kositchaiwat C, Kositchaiwat S, Havanondha J. Curcuma longa Linn. in the treatment of
gastric ulcer comparison to liquid antacid: a controlled clinical trial. J Med Assoc Thai 1993;
76:601-5.

10. Deodhar SD, Sethi R, Sriimal RC. Preliminary study on antirheumatic activity of


12. Polasa K, Raghuram TC, Krishna TP, Krishnaswamy K. Effect of turmeric on urinary

13. Azuine MA, Bhide SV. Chemopreventive effect of turmeric against stomach and skin

occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer.

15. Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. Therapeutic potential of curcumin in
human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits

16. Huang MT, Deschner EE, Newmark HL, Wang ZY, Ferraro TA, Conney AH. Effect of
dietary curcumin and ascorbyl palmitate on azoxymethanol-induced colonic epithelial cell

17. Subramanian M, Sreejayan Rao MN, Devasagayam TP, Singh BB. Diminution of singlet
oxygen-induced DNA damage by curcumin and related antioxidants. Mutat Res 1994; 311:249-
55.

18. Soni KB, Kuttan R. Effect of oral curcumin administration on serum peroxides and


VALERIAN

*Valeriana officinalis*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Amantilla, all-heal, baldrian, baldrianwurzel, Belgium valerian, common valerian, fragrant valerian, garden heliotrope, garden valerian, Indian valerian, Mexican valerian, Pacific valerian, valeriana, *Valeriana officinalis, Valeriana rhizome, Valerianae radix*, valeriane

INDICATIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>B1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>B2</td>
</tr>
<tr>
<td>Sedation</td>
<td>B2</td>
</tr>
<tr>
<td>Sleep quality and quantity (with lemon balm)</td>
<td>B2</td>
</tr>
<tr>
<td>Mental stress (with kava)</td>
<td>B2</td>
</tr>
<tr>
<td>Fibromyalgia (as a bath)</td>
<td>B2</td>
</tr>
<tr>
<td>Anxiety (with passion flower)</td>
<td>C</td>
</tr>
<tr>
<td>Anxiety (with St. John’s wort)</td>
<td>C</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>C</td>
</tr>
</tbody>
</table>

PREGNANCY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-teratogenic</td>
<td>2</td>
</tr>
</tbody>
</table>
According to a study on adverse effects of intoxication during pregnancy, there are no reports of teratogenic activity from valerian intoxication during pregnancy\textsuperscript{17}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{18}</td>
</tr>
<tr>
<td>May retard ossification\textsuperscript{18}</td>
</tr>
</tbody>
</table>

In rats, 30-day administration of the valepotriate constituents of valerian did not change the average length of estral cycle, nor the number of estrous phases during this period, nor the fertility index\textsuperscript{18}. No changes were detected in the development of the offspring after treatment during pregnancy\textsuperscript{18}. No signs of fetotoxicity or external malformations were observed, although internal examination revealed an increase in number of retarded ossification at higher doses\textsuperscript{18}.

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Cytotoxic and mutagenic\textsuperscript{19, 20}</td>
</tr>
</tbody>
</table>

Valepotriates have been shown to be cytotoxic and mutagenic \textit{in vitro}\textsuperscript{19, 20}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Unknown</td>
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</table>

There are no reports in the evidence-based scientific literature of valerian being either safe or contraindicated during lactation.

**CONTRAINDICATION**

Surgery\textsuperscript{21}

**CAUTION**

Driving or operating heavy machinery\textsuperscript{22}
Liver disease\textsuperscript{23}

**CONSTITUENTS**

Valepotriates\textsuperscript{23}: valtrate, isovaltrate, didrovaltrate

Volatile oils\textsuperscript{23}: kessanes, valerenal, valeranone, valeric acid

Monoterpenes\textsuperscript{24, 25}: berneol

Sesquiterpenes\textsuperscript{24, 25}: valerenic acid, valerenone, kessyl glycol

Lignans\textsuperscript{24}

**GABA**\textsuperscript{24}

**TOXICITY**

$LD_{50}$ of essential oil (intraperitoneal)\textsuperscript{26}: 15g/kg

$LD_{50}$ of valerenic acid (intraperitoneal)\textsuperscript{26}: 300mg/kg

$LD_{50}$ of valepotriate constituents (intraperitoneal)\textsuperscript{22}: 64-150mg/kg

Valepotriates were not found to be toxic at 4.6g/kg orally in mice\textsuperscript{22}

Valepotriates are poorly absorbed and subject to a significant first pass effect\textsuperscript{27}. As such, they are quickly degraded to less toxic metabolites and are not likely to cause acute adverse reactions\textsuperscript{24}.

**PHARMACOLOGY**

Valerian has sedative, anxiolytic, antidepressant, anticonvulsant, hypotensive and antispasmodic effects\textsuperscript{12, 25, 28}.

The valepotriate constituents were shown to decrease benzodiazepine withdrawal and to bind dopamine receptors\textsuperscript{24, 25}.

The constituents valerenic acid and kessyl glycol were shown to cause sedation in animals\textsuperscript{24}. 
Valerenic acid may inhibit the enzyme system responsible for the catabolism of GABA, thereby increasing GABA concentrations and decreasing central nervous system (CNS) activity\(^1\).

The lignans and GABA constituents in valerian may contribute to its sedative effect\(^2\).

Valerian does not appear to cause adverse effects with respect to reaction time, alertness, and concentration the morning after intake\(^3\).

In healthy elderly people, valerian does not appear to affect psychomotor performance\(^4\).

Valerian may affect the cytochrome P450 CYP3A4 enzyme\(^5\).

**DRUG INTERACTIONS**\(^1\)

Alcohol\(^6\)

Barbiturates\(^2\)

Benzodiazepines\(^2\)

Drugs metabolized by cytochrome CYP3A4\(^2\)

Sedative drugs\(^2\)

**PART USED**\(^1\)

Root

**REFERENCES**


WILD YAM

*Dioscorea villosa*

SYNONYMS/COMMON NAMES/RELATED COMPOUNDS

Atlantic yam, barbasco, China root, colic root, devil's bones, dioscorea, *Dioscoreae*, Mexican yam, natural DHEA, phytoestrogen, rheumatism root, wild Mexican yam, yam, yuma

INDICATIONS

Oral

| Menopausal symptoms (with burdock root, licorice root, motherwort, and angelica root) | B2 |
| Hyperlipidemia | D |
| Unproven hormonal effects | D |

Topical

| No effect on menopausal symptoms | B1 |
| Unproven hormonal effects | B1 |

PREGNANCY

| Uterine stimulant | 4 |

Wild yam is believed to induce uterine contractions. There are no reports in the evidence-based medicine literature of wild yam causing uterine contractions.
Cream

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Wild yam products may contain synthetic progesterone&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Commercial wild yam products may contain synthetic progesterone and therefore have hormonal effects<sup>7</sup>.

Diosgenin

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Non-teratogenic&lt;sup&gt;8,9&lt;/sup&gt;</td>
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</tbody>
</table>

Animal studies have reported that diosgenin, a constituent of wild yam, is non-teratogenic<sup>8,9</sup>.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Unknown</td>
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</table>

There are no reports in the evidence-based medicine literature of wild yam being either safe or contraindicated during lactation.

Cream

<table>
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<tbody>
<tr>
<td>Wild yam products may contain synthetic progesterone&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Commercial wild yam products may contain synthetic progesterone and therefore have hormonal effects<sup>7</sup>.
CONSTITUENTS

Saponins\(^4,10\): diosgenin, dioscin

Alkaloid\(^4,10\): dioscorin

TOXICITY

LD\(_{50}\) of aqueous fraction: 1.4 g/kg (mice)\(^{11}\)

LD\(_{50}\) of dioscoretine: 0.58 g/kg (mice)\(^{11}\)

PHARMACOLOGY

Diosgenin is a steroid precursor that was used in the first pharmaceutical manufacture of oral contraceptives, topical hormones, systemic corticosteroids, androgens, estrogens, progesterone, and other sex hormones\(^{12-14}\).

The chemical conversion of diosgenin into estrogen, progesterone, or any other steroidal compound has not been demonstrated in the human body\(^{12}\).

Topical application of wild yam has not been shown to affect serum levels of follicular stimulating hormone (FSH), estradiol, or progesterone\(^5\).

Oral administration of wild yam did not increase serum dehydroepiandrosterone sulfate (DHEA-S) levels\(^4,15\).

Wild yam has been shown to enhance estradiol binding to estrogen receptors and to induce transcription activity in estrogen-responsive cells\(^16\).

Diosgenin may stimulate the growth of mammary tissue\(^17\).

The saponins, namely dioscin, are gastrointestinal irritants\(^{18}\).

DRUG INTERACTIONS\(^7\)

Non Steroidal Anti-inflammatory Drugs (NSAIDs)\(^{19}\)

Hormone Replacement Therapy (HRT)/oral contraceptives\(^{20}\)
insulin/oral hypoglycemic agents

Fibric acid derivatives

Cholesterol-lowering agents

PARTS USED

Root and rhizome

REFERENCES


YARROW

*Achillea millefolium*

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Achilee, achillea, acuilee, band man's plaything, bauchweh, birangasifa, bloodwort, carpenter's weed, civan percemi, common yarrow, devil's nettle, devil's plaything, erba da cartentieri, erba da falegname, gemeine schafgarbe, green arrow, herbe aux charpentiers, katzenkrat, milefolio, milfoil, millefeuille, millefolii flos, millefolii herba, millefolium, millegoglie, noble yarrow, nosebleed, old man's pepper, roga mari, sanguinary, soldier's wound wort, staunchweed, tausendaugbram, thousand-leaf, wound wort

INDICATIONS

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitation following chronic hepatitis</td>
<td>E</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>E</td>
</tr>
<tr>
<td>Blood sugar regulation</td>
<td>E</td>
</tr>
<tr>
<td>Diuretic</td>
<td>E</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>E</td>
</tr>
<tr>
<td>Anti-coagulant activity</td>
<td>E</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>E</td>
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</table>
## PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Reduces fetal weight$^9$</td>
<td>3</td>
</tr>
<tr>
<td>Increases placental weight$^9$</td>
<td>3</td>
</tr>
</tbody>
</table>

When administered to pregnant rats at 56 times the human dose, yarrow was associated with reduced fetal weight and increased placental weight$^9$.

<table>
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<tbody>
<tr>
<td>Neurotoxic component (thujone)$^{10}$</td>
<td>3</td>
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</table>

The yarrow constituent thujone is neurotoxic, where it was found to cause convulsions in the central nervous system of rats$^{10}$.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Porphyrogenic component (thujone)$^{11}$</td>
<td>3</td>
</tr>
</tbody>
</table>

The yarrow constituent thujone is porphyrogenic and may be hazardous to patients with underlying defects in hepatic heme synthesis$^{11}$.

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Weakly genotoxic$^{12}$</td>
<td>3</td>
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</table>

Yarrow tea was weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster*$^{12}$.

<table>
<thead>
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<th>Level</th>
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<tbody>
<tr>
<td>May interfere with spermatogenesis$^{13}$</td>
<td>3</td>
</tr>
</tbody>
</table>
A study showed that when Swiss mice where exposed to ethanolic and hydroalcoholic extracts of *Achillea* flowers, observations of spermatogenesis showed exfoliation of immature germ cells, germ cell necrosis and seminiferous tubule vacuolization\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential abortifacient\textsuperscript{14,15}</td>
</tr>
<tr>
<td>Emmenagogue\textsuperscript{14}</td>
</tr>
</tbody>
</table>

A review article on the potential value of plants as sources of anti-fertility agents reported that yarrow was a potential abortifacient and an emmenagogue\textsuperscript{14}.

**LACTATION**

<table>
<thead>
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<th>Level</th>
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<tbody>
<tr>
<td>Neurotoxic component (thujone)\textsuperscript{10}</td>
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The yarrow constituent thujone is neurotoxic, where it was found to cause convulsions in the central nervous system of rats\textsuperscript{10}.

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<tbody>
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<td>Porphyrogenic component (thujone)\textsuperscript{11}</td>
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The yarrow constituent thujone is porphyrogenic and may be hazardous to patients with underlying defects in hepatic heme synthesis\textsuperscript{11}.

<table>
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<tbody>
<tr>
<td>Weakly genotoxic\textsuperscript{12}</td>
</tr>
</tbody>
</table>

Yarrow tea was weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster*\textsuperscript{12}. 
CAUTION

Epilepsy\textsuperscript{15}

TOXIC CONSTITUENTS

Volatile oils\textsuperscript{8,15}: chamazulene, thujone (trace amounts) and other azulenes

Polyunsaturated alkamides\textsuperscript{16}

Sesquiterpenoids\textsuperscript{17}: achimillic acids (A, B C)

Alkaloid\textsuperscript{7}: achilleine

TOXICITY

LD\textsubscript{50} in mice (oral)\textsuperscript{15}: 3.65 g/kg

PHARMACOLOGY

In diabetic mice and rats, yarrow was shown to have marked hypoglycemic and glycogen-sparing properties\textsuperscript{4}.

The polyunsaturated alkamides from Achillea species were shown to have anti-inflammatory activity where they inhibited cyclooxygenase and 5-lipoxygenase assays \textit{in vitro}\textsuperscript{16}.

The sesquiterpenoids constituents achimillic acids A, B and C from yarrrw were shown to have anti-tumour activity against mouse P-388 leukemia cells \textit{in vivo}\textsuperscript{17}.

The volatile oil of yarrow was reported to have a depressant activity on the central nervous system\textsuperscript{15}.

The alkaloid constituent achilleine was found to decrease blood clotting time in rabbits\textsuperscript{7}.

Yarrow showed some evidence of diuretic activity\textsuperscript{5}.

Yarrow has moderate antibacterial activity\textsuperscript{6}.
Persons allergic to the Asteraceae family may exhibit allergic reactions, such as contact dermatitis, when exposed to yarrow. Alpha-peroxyachifolid was identified as the contact allergen in yarrow.

Yarrow alkaloids were reported to have hypotensive properties.

**DRUG INTERACTIONS**

Antacids

Anticoagulants and antiplatelets

Barbiturates

Hypertensive or hypotensive therapy

Proton pump inhibitors

**PARTS CONTAINING TOXINS**

Flower head

**References**


20. Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of Compositae plants. Contact Dermatitis 1993; 29:6-10.


Chapter 5 Vitamins

Vitamins are frequently taken by the general public to correct nutritional deficiencies and to prevent disease. In pregnancy, vitamins are often taken to help with the symptoms of pregnancy (vitamin B6 for nausea), to help prevent anemia (vitamin B12) and to support newborn blood clotting (vitamin K). In the case of some vitamins, such as vitamin A, too high of a dose may be associated with teratogenic effects.

In selecting the 8 vitamins to review, we focused on the vitamins that would support the common deficiencies of pregnancy and lactation and the vitamins that, in elevated doses, may have harmful effects to the mother or fetus. All 8 reviews are presented as follows:

**Vitamin Name**

Name of the vitamin.

**Pregnancy**

The safety of this herb during pregnancy. According to evidence-based medicines principles, the safety of this herb during pregnancy is evaluated based on grades of evidence (see Methodology section).

**Lactation**

The safety of this herb during lactation. According to evidence-based medicines principles, the safety of this herb during lactation is evaluated based on grades of evidence (see Methodology section).

**VITAMIN A**

**PREGNANCY**

<table>
<thead>
<tr>
<th>May reduce maternal mortality and morbidity&lt;sup&gt;1&lt;/sup&gt;</th>
<th>1a</th>
</tr>
</thead>
</table>
A systematic review was conducted on the effect of vitamin A supplementation during pregnancy and how it improves maternal mortality and morbidity\(^1\). In 5 trials involving 23,426 women, weekly vitamin A supplementation resulted in a reduction in maternal mortality up to 12 weeks postpartum and a reduction in night blindness\(^1\).

<table>
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<tr>
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<tbody>
<tr>
<td>Non-teratogenic at 6,000 IU per day(^2)</td>
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</table>

A clinical trial showed that daily intake of 6,000 IU of vitamin A during pregnancy did not increase the incidence of fetal malformations\(^2\).

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Conflicting evidence</td>
</tr>
</tbody>
</table>

| Potentially teratogenic >10,000 IU per day\(^3-5\) | 1b |
| Potentially non-teratogenic at doses >8000 IU or >10,000 IU per day\(^5,6\) | 1c |

There is conflicting evidence as to the teratogenicity of vitamin A during pregnancy\(^5\). A prospective cohort study of 22,748 pregnant women found that 339 had babies with birth defects; 121 of these babies had defects occurring in sites that originated in the cranial neural crest, which are associated with vitamin A teratogenicity\(^4\). A higher prevalence of cranial neural crest defects was found in women consuming >15,000 IU and >10,000 IU of vitamin A per day than in women consuming only 5,000 IU\(^4\). The increased frequency of defects was concentrated among the babies born to women who had consumed high levels of vitamin A before the seventh week of gestation\(^4\). Among the babies born to women who took more than 10,000 IU of preformed vitamin A per day in the form of supplements, it was estimated that about 1 infant in 57 had a malformation attributable to the supplement\(^4\).

Another case-control study of 1,000 livebirths reported that a teratogenic effect might exist for exposures to high doses of vitamin A (>40,000 IU), particularly during the first 3 months of pregnancy\(^3\).
On the other hand, a case-control study on 955 offsprings with either major malformations or neural tube defects found no association between periconceptional vitamin A exposure at doses >8000 IU or >10,000 IU per day and malformations in general, cranial neural crest defects, or neural tube defects⁶.

<table>
<thead>
<tr>
<th>Potential liver toxicity at 25,000 IU/day over long periods⁷</th>
<th>1c</th>
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</thead>
</table>

Vitamin A hepatotoxicity was reported in 41 patients⁷. The smallest continuous daily consumption leading to cirrhosis was 25,000 IU during 6 years, whereas higher daily doses (greater than or equal to 100,000 IU) taken during 2.5 years resulted in liver damage⁷.

Retinoic acid

<table>
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<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Teratogenic⁸</td>
</tr>
<tr>
<td>Retinoic acid syndrome⁸</td>
</tr>
</tbody>
</table>

Retinoic acid, an analogue of vitamin A, was shown to be teratogenic and lead to a characteristic pattern of malformation involving craniofacial, cardiac, thymic, and central nervous system structures called “retinoic acid syndrome”⁸. These malformations included microtia/anotia, micrognathia, cleft palate, conotruncal heart defects and aortic-arch abnormalities, thymic defects, retinal or optic-nerve abnormalities, and central nervous system malformations⁸. The malformations are believed to result from the action of retinoic acid on cranial neural crest cells⁹.
Mother-to-Child HIV transmission

<table>
<thead>
<tr>
<th>Vitamin A 5,000IU and 200,000 IU of beta-carotene daily</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May reduce mother-to-child HIV transmission in preterm births(^\text{10})</td>
<td>1a</td>
</tr>
<tr>
<td>Decreases incidence of preterm delivery(^\text{10})</td>
<td>1a</td>
</tr>
<tr>
<td>Vitamin A 5,000 IU daily</td>
<td>Level</td>
</tr>
<tr>
<td>No effect of preterm delivery(^\text{11})</td>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 728 pregnant HIV-positive women found that a daily dose of 5000 IU of vitamin A and 200,000 IU of beta-carotene reduced the incidence of preterm delivery\(^\text{10}\). Among the preterm deliveries, newborns born to mothers taking vitamin A were less likely to be infected with HIV\(^\text{10}\).

In a randomized controlled trial of 1,075 HIV-positive pregnant women, vitamin A supplementation did not affect newborn death rate or preterm delivery\(^\text{11}\).

<table>
<thead>
<tr>
<th>Conflicting evidence</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May increase mother-to-child HIV transmission(^\text{12})</td>
<td>1a</td>
</tr>
<tr>
<td>No effect on mother-to-child HIV transmission(^\text{10,13,14})</td>
<td>1a</td>
</tr>
<tr>
<td>No effect of HIV immunologic markers (CD4, CD8, and CD3 counts)(^\text{11})</td>
<td>1a</td>
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</tbody>
</table>

A randomized controlled trial of 1,078 HIV-infected pregnant African women found that vitamin A supplementation increased the risk of mother-to-child HIV transmission\(^\text{12}\).
Two randomized controlled trials, however, one involving 697 HIV-positive pregnant African women and another involving 728 HIV-positive African women, found that vitamin A supplementation (daily dose of 10,000 IU and 5,000 IU, respectively) did not affect mother-to-child HIV transmission\textsuperscript{10,13}. In a randomized controlled trial of 1,075 HIV-positive pregnant African women, vitamin A supplementation did not affect immunologic markers (CD4, CD8, and CD3 counts) associated with HIV\textsuperscript{11}.

A cohort study of 95 HIV-1-infected pregnant women living in the United States found that vitamin A deficiency was rare in the United States and that serum retinol levels were not associated with risk of vertical HIV-1 transmission\textsuperscript{14}. The researchers recommended that pregnant HIV-1-infected women living in nations where vitamin A deficiency is not a public health problem should not be advised to take extra vitamin A supplements due to possible teratogenic effects\textsuperscript{14}.

**Deficiency**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low levels in habitual abortion\textsuperscript{15}</td>
</tr>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

A study of 40 women with habitual abortions showed that vitamin A levels were significantly lower in women with habitual abortions than in controls\textsuperscript{15}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{16,17}</td>
</tr>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 100 mothers having uncomplicated deliveries showed that receiving 200,000 IU of vitamin A orally soon after delivery improved vitamin A intake of breastfed infants during the first 3 months\textsuperscript{16}. No adverse effects were reported\textsuperscript{16}.

Another randomized controlled trial of 220 women showed that a single dose of 200,000 IU of vitamin A at 1-3 week postpartum did not result in any adverse effects\textsuperscript{17}.
May increase HIV transmission via breastfeeding from HIV-positive mothers\textsuperscript{12} & 1a \\

Did not affect infant mortality\textsuperscript{12} & 1a

A randomized controlled trial of 1,078 HIV-positive pregnant women found that vitamin A supplementation increased the risk of HIV breastfeeding transmission\textsuperscript{12}. The study also found that vitamin A supplementation had no effect on infant mortality by 24 months\textsuperscript{12}.

Potential liver toxicity at 25,000 IU/day over long periods\textsuperscript{7} & 1c

Vitamin A hepatotoxicity was reported in 41 patients\textsuperscript{7}. The smallest continuous daily consumption leading to cirrhosis was 25,000 IU during 6 years, whereas higher daily doses (greater than or equal to 100,000 IU) taken during 2.5 years resulted in liver damage\textsuperscript{7}.

**VITAMIN D**

**Pregnancy**

Not enough evidence to evaluate\textsuperscript{18} & 1a

A systematic review was conducted to assess the effects of vitamin D supplementation on pregnancy outcome\textsuperscript{18}. Two trials involving 232 women were included in this study where in one trial the mothers had higher mean daily weight gain and lower number of low birthweight infants, and in the other trial the supplemented group had lower birthweights\textsuperscript{18}. The researchers concluded that there is not enough evidence to evaluate the effects of vitamin D supplementation during pregnancy\textsuperscript{18}. 
<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk\textsuperscript{19,20}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial was conducted to evaluate the effects of single-dose (5 mg at the seventh month) and daily vitamin D supplementation (1,000 IU/day) in pregnant women during the last trimester\textsuperscript{19}. No adverse effects or significant modification of maternal calciuria or of the birth weight of term infants was observed\textsuperscript{19}.

A randomized controlled trial of 30 low birth weight infants, 35 infants with perinatal asphyxia, and 16 infants of diabetic mothers showed no adverse effects associated with vitamin D supplementation\textsuperscript{20}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Crosses the palcenta\textsuperscript{21}</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4</td>
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</tbody>
</table>

According to one study, the fetus is entirely dependent on the mother for its supply of vitamin D (25 hydroxyvitamin D) which is believed to easily cross the placenta\textsuperscript{21}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk when used below 2,000 IU (50 mcg) per day\textsuperscript{22}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

According to the Institute of Medicine, vitamin D is safe during pregnancy when used in amounts below 2,000 IU (50 mcg) per day\textsuperscript{23}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Risk of hypercalcemia at &gt; 2,000 IU (50 mcg) per day\textsuperscript{23}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

According to the Institute of Medicine, daily intake of vitamin D above 2,000 IU (50 mcg) may lead to hypercalcemia\textsuperscript{23}. In pregnancy, hypercalcemia can lead to suppression of parathyroid hormone, hypocalcemia, tetany, seizures, aortic valve stenosis, retinopathy, and mental and/or physical retardation in the infant\textsuperscript{23}.
Deficiency

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>May develop hypocalcemia&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

In a study of 120 pregnant women, 75 women who did not take any vitamin D supplements during pregnancy showed statistically significant hypocalcaemia, hypophosphatemia and elevation of heat-labile alkaline phosphatase (HLAP)<sup>24</sup>.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Minimum intake of 200 IU per day for infant&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

According to the National Academy of Sciences, it is recommended that all infants, including those who are exclusively breastfed, have a minimum intake of 200 IU of vitamin D per day beginning during the first 2 months of life<sup>25</sup>. In addition, it is recommended that an intake of 200 IU of vitamin D per day be continued throughout childhood and adolescence, because adequate sunlight exposure is not easily determined for a given individual<sup>25</sup>.

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Minimal risk when used below 2,000 IU (50 mcg) per day&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

According to the Institute of Medicine, vitamin D is safe during lactation when used in amounts below 2,000 IU (50 mcg) per day<sup>23</sup>.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of hypercalcemia at &gt; 2,000 IU (50 mcg) per day&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

According to the Institute of Medicine, daily intake of vitamin D above 2,000 IU (50 mcg) may lead to hypercalcemia<sup>23</sup>. 
**VITAMIN E**

**PREGNANCY**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk at 400 IU per day(^{26})</td>
</tr>
<tr>
<td>May prevent pre-eclampsia (with vitamin C)(^{26})</td>
</tr>
</tbody>
</table>

A randomized controlled trial on the effect of supplementation with vitamin E and C in 283 pregnant women with pre-eclampsia showed no adverse effects with daily doses of 400 IU of vitamin E at weeks 16-22 of gestation\(^{26}\). The combination of vitamin E and C was also shown to be beneficial in the prevention of pre-eclampsia\(^{26}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion associated with blood levels above 0.50mg/100 ml(^{27})</td>
</tr>
</tbody>
</table>

In a group of 50 spontaneously aborting women compared with the same number of pregnant women whose pregnancies terminated uneventfully, a significantly higher percentage of aborting women had individual values of serum alpha-tocopherol above the 0.50 mg/100 ml normal limit\(^{27}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases malformations(^{28-30})</td>
</tr>
</tbody>
</table>

Maternal dietary treatment with vitamin E markedly reduced the severity of malformations in diabetic rats\(^{28-30}\).
Animal studies have shown that vitamin E does not have mutagenic, teratogenic nor carcinogenic properties\(^{31,32}\). In human studies, oral vitamin E supplementation resulted in few side effects even at doses as high as 3,200 mg/day\(^{31,32}\).

Pregnant rats receiving large doses of vitamin E (22.5 to 2,252 mg/kg per day) had larger livers, higher levels of lipids and vitamin E in plasma, and higher concentrations of vitamin E in the livers than did controls\(^{33}\). The researchers reported no obvious teratogenic effects in the newborn young of the vitamin E-supplemented rats, although some eye abnormalities were seen in the older pups of rats given extremely high amounts of the vitamin\(^{33}\). The survival rate, weight of the pups, and litter size were unaffected by vitamin E supplementation\(^{33}\).

According to a compendium on the safety of drugs during pregnancy and lactation, no adverse effects were reported with oral intake of 600-900 IU of vitamin E daily during the last two months of pregnancy\(^{34}\).
Deficiency

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Low levels in habitual abortion\textsuperscript{15}</td>
</tr>
</tbody>
</table>

A study of 40 women with habitual abortion (HA) and controls showed that vitamin E levels were significantly lower in women with HA than in controls\textsuperscript{15}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>Crosses into breast milk\textsuperscript{33, 35}</td>
</tr>
<tr>
<td>2</td>
<td>Minimal risk\textsuperscript{36}</td>
</tr>
</tbody>
</table>

Orally administered alpha-tocopherol (1.1 g) reached a maximum value of 414 micrograms/100 g in human breast milk, which was 6.6-fold the pre-supplemental level, after three days and declined to the base line level after five days\textsuperscript{35}. A case study of a pregnant women mega-dosing vitamin E showed breast milk vitamin E levels more than three times the upper range of normal\textsuperscript{36}. No adverse effects were reported\textsuperscript{36}. In a study of pregnant rats receiving large doses of vitamin E (22.5 to 2,252 mg/kg per day), mammary transfer of vitamin E was found to be quite efficient\textsuperscript{33}.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Does not interfere with milk production\textsuperscript{33, 37-39}</td>
</tr>
<tr>
<td>3</td>
<td>Does not adversely affect milk composition\textsuperscript{33, 37-39}</td>
</tr>
</tbody>
</table>

There are numerous animal studies on the transfer of vitamin E into breast milk and vitamin E supplementation in cattle. None of these studies reported that vitamin E supplementation interfered with milk production or negatively affected milk composition\textsuperscript{33, 37-39}. 
### VITAMIN K

#### PREGNANCY

<table>
<thead>
<tr>
<th>Level</th>
<th>Treatment of hemolytic disease of the newborn[^40]</th>
<th>Improves indices of coagulation[^40]</th>
</tr>
</thead>
</table>

A systematic review concluded that a single dose (1.0 mg) of intramuscular vitamin K after birth is effective in the prevention of classic hemolytic disease of the newborn[^40]. Either intramuscular or oral (1.0 mg) vitamin K prophylaxis improves biochemical indices of coagulation status at 1-7 days[^40].

<table>
<thead>
<tr>
<th>Level</th>
<th>Does not prevent periventricular hemorrhage in preterm infants[^41]</th>
</tr>
</thead>
</table>

A systematic review found that vitamin K administered to women at risk of imminent preterm birth did not significantly prevent periventricular hemorrhage in preterm infants[^41].

<table>
<thead>
<tr>
<th>Level</th>
<th>In preterm pregnancies, slow and limited placental transport[^42]</th>
</tr>
</thead>
</table>

A randomized controlled trial of 78 women with preterm pregnancies showed that vitamin K1 crosses the placenta slowly and to a limited degree[^42].

<table>
<thead>
<tr>
<th>Level</th>
<th>In low birth weight and &lt;32 weeks gestation infants, supplementation during pregnancy may not affect coagulation parameters[^43]</th>
</tr>
</thead>
</table>

A prospective cohort study of 33 women showed that maternal supplementation with vitamin K1 had no significant effect on the level of vitamin K-dependent factors in low birth weight and <32 weeks gestation infants[^43].

[^40]: Reference Number
[^41]: Reference Number
[^42]: Reference Number
[^43]: Reference Number
<table>
<thead>
<tr>
<th>Conflicting evidence</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No association with acute lymphoblastic leukaemia or cancer(^{44-46})</td>
<td>1b</td>
</tr>
<tr>
<td>Potential risk of acute lymphoblastic leukaemia or cancer with intramuscular vitamin K(^{47-49})</td>
<td>1b</td>
</tr>
<tr>
<td>Minimal risk of cancer with oral vitamin K(^{48})</td>
<td>1b</td>
</tr>
</tbody>
</table>

A cohort study of 177 cases and 354 age- and sex-matched controls showed no relation between childhood acute lymphoblastic leukaemia and neonatal administration of intramuscular vitamin K\(^{44}\). A case control study found no significant association between parenteral vitamin K prophylaxis and leukemia or tumours\(^{45}\). Another case control study of 54,795 children born from 1959 through 1966 found no association between exposure to vitamin K and an increased risk of any childhood cancer or of all childhood cancers combined\(^{46}\).

A retrospective case-control study on 16,193 infants delivered in Great Britain in one week of April 1970 showed an association between cancer incidence and the prophylactic administration of vitamin K\(^{49}\). A cohort study of 195 children diagnosed with cancer from 1971 to 1991, matched with 558 controls, found a significant association with intramuscular vitamin K and cancer when compared with oral vitamin K or no vitamin K therapy\(^{48}\). There was no significant increase in risk for children who had been given oral vitamin K when compared with no vitamin K\(^{48}\). The researchers concluded that the prophylactic benefits against hemorrhagic disease are unlikely to exceed the potential adverse effects from intramuscular vitamin K\(^{48}\). A review article reported that vitamin K administration to newborns may increase the risk of acute lymphoblastic leukemia in childhood\(^{47}\).
<table>
<thead>
<tr>
<th>Level</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Poor transport to the fetus</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Good transport to placenta</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Intravenous injection of vitamin K2 into mothers was shown to be actively incorporated into placental tissue, while transfer of vitamin K2 to fetal blood (cord blood) was small\(^51\). An in vitro investigation of vitamin K2 transport using human placental villous tissues found that the transport of vitamin K1 into the fetus is not especially pronounced, but transport into the placental villous tissue is comparatively good\(^50\).

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Non-mutagenic</td>
<td>3</td>
<td></td>
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</tbody>
</table>

High concentrations of vitamin K(1) did not induce primary DNA damage in cells from rat embryos grown in vitro\(^52\).

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Minimal risk</td>
<td>4</td>
<td></td>
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</table>

According to the Food and Nutrition Board, Institute of Medicine, there is no evidence to suggest that vitamin K intake for pregnant women should be different from that for non-pregnant women\(^53\).

Deficiency

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K Deficiency Bleeding</td>
<td>1b</td>
<td></td>
</tr>
</tbody>
</table>
A stratified cluster sampling of 28,156 live newborns from five districts and six counties in China found that vitamin K deficiency bleeding (VKDB) was 3.27 per thousand\textsuperscript{54}. VKDB was higher in the rural areas than in the urban areas, in breast-fed babies and in pre-term babies\textsuperscript{54}.

<table>
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<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Anticonvulsant therapy may cause deficiency\textsuperscript{55}</td>
</tr>
</tbody>
</table>

A multicenter observational case-control study of 25 pregnant women receiving anticonvulsant therapy and 25 pregnant controls found that the incidence of vitamin K deficiency was increased in neonates exposed to anticonvulsant drugs prenatally\textsuperscript{55}.

<table>
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<tr>
<th>Level</th>
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<tbody>
<tr>
<td>May be secondary to hyperemesis gravidum\textsuperscript{56}</td>
</tr>
</tbody>
</table>

A case of a woman at 15 weeks gestation with hyperemesis gravidarum complicated by an episode of severe epistaxis was associated with a coagulopathy secondary to vitamin K deficiency\textsuperscript{56}. The coagulopathy resolved after vitamin K replacement\textsuperscript{56}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Breast-fed infants appear to be vitamin K deficient up to 3 months after birth\textsuperscript{57,58}</td>
</tr>
</tbody>
</table>

In comparison to bottle-fed infants, breast-fed infants appear to be vitamin K deficient from 1 to 3 months after birth\textsuperscript{57,58}. Breast-fed infants receiving no vitamin K at birth were more deficient in vitamin K at 3 months then breast-fed infants having received vitamin K prophylaxis\textsuperscript{58}. Based on these results, routine vitamin K prophylaxis after birth for all breast-fed infants was recommended\textsuperscript{58}. 


In an outcome study of 60 puerperal women, the continuous administration of menaquinone-4 (MK-4) to mothers was shown to increase the concentration of vitamin K in milk, preventing idiopathic vitamin K deficient bleeding in infants\(^{59}\). MK-4 was shown to be accumulated and concentrated into breast milk\(^{59}\).

In a longitudinal study of 23 lactating mothers, there was no significant correlation between phylloquinone intake and breast milk concentration at 6, 12, and 26 weeks\(^{60}\).

Vitamin K is present in very low concentrations in human milk\(^{62}\). A cross-sectional study of 15 mothers from day 1 to 6 months postpartum showed that vitamin K levels between colostrum and mature milk at 6 months were not statistically significant\(^{61}\). Because of significantly increased volumes of milk over the lactation period, however, approximately twice as much vitamin K was delivered in mature milk than in colostrum\(^{61}\). Based on these results, the researchers concluded that vitamin K in human milk is insufficient to meet recommended intakes for infants aged less than 6 months\(^{61}\).

<table>
<thead>
<tr>
<th>Level</th>
<th>Vitamin K administration and breast milk vitamin K concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Continuous menaquinone-4 (MK-4) administration increases vitamin K in breast milk</td>
</tr>
<tr>
<td>1c</td>
<td>Phylloquinone administration may not affect breast milk concentration(^{60})</td>
</tr>
<tr>
<td>1c</td>
<td>Low levels in breast milk(^{61-63})</td>
</tr>
</tbody>
</table>

\(^{59}\) For phytochemical mechanisms of vitamin \(K\) absorption and \(K\) action. \(^{60}\) A longitudinal study of 23 lactating mothers. \(^{61}\) Vitamin K is present in very low concentrations in human milk. \(^{62}\) A cross-sectional study of 15 mothers from day 1 to 6 months postpartum. \(^{63}\) Based on these results, the researchers concluded that vitamin K in human milk is insufficient to meet recommended intakes for infants aged less than 6 months.
Breast-fed infants may be at risk of late onset hemorrhagic disease of the newborn\textsuperscript{64, 65}.

Four cases of infants with acute bleedings due to vitamin K-deficiency beyond the neonatal period were reported\textsuperscript{64}. Two of these infants had intracranial hemorrhages and died\textsuperscript{64}. All infants were breast-fed, born appropriate for date and did not receive vitamin K-prophylaxis\textsuperscript{64}. In a different study, another 4 cases of hemorrhages in breast-fed infants were reported\textsuperscript{65}. In all cases, the infants were males, between 4 to 6 weeks old and in 2 of these cases, a hemorrhage in the central nervous system was involved\textsuperscript{65}. There was a prompt improvement after administration of vitamin K\textsuperscript{65}.

Intravenous injection of vitamin K2 into mothers was shown to increase the release of vitamin K2 into milk with time even after the plasma vitamin K2 concentration in maternal blood decreased\textsuperscript{51}.

High concentrations of vitamin K(1) did not induce primary DNA damage in cells from rat embryos grown in vitro\textsuperscript{52}.
According to the Food and Nutrition Board, Institute of Medicine, there is no evidence to suggest that vitamin K intake for breastfeeding women should be different from that of non-breastfeeding women\textsuperscript{53}.

**Oral Administration to infants**

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Prevents vitamin K deficiency bleeding in healthy breastfed infants\textsuperscript{66, 67}</td>
</tr>
</tbody>
</table>

A prospective clinical trial found that 1 mg per week or 25 mcg per day of vitamin K1 proved to be effective in preventing vitamin K deficiency bleeding in healthy breastfed infants\textsuperscript{66}. The oral administration of vitamin K1 1 mg, repeated weekly during the first three months of life, was shown to offer complete protection against vitamin K deficiency in 48 healthy breast-fed infants and did not result in an accumulation of vitamin K1 in the blood\textsuperscript{67}.

**FOLIC ACID**

**PREGNANCY**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves hemoglobin levels and folate status\textsuperscript{68}</td>
</tr>
</tbody>
</table>

A systematic review of 21 studies showed that folate supplementation during pregnancy appears to improve hemoglobin levels and folate status\textsuperscript{68}.

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Prevents neural tube defects\textsuperscript{69-71}</td>
</tr>
<tr>
<td>Prevents recurrence of neural tube defects in woman with one child with neural tube defects\textsuperscript{69}</td>
</tr>
</tbody>
</table>

The United States Food and Drug Administration (FDA) recommends folic acid supplementation at 800mcg daily in order to reduce the risk of neural tube defects\textsuperscript{71}. A randomized controlled
trial of 293 women found that a fortification program that delivered between 200 and 400 micrograms of folic acid daily to women would protect against neural tube defects\textsuperscript{70}.

A randomized controlled trial of 111 women who had one child with a neural-tube defect found that 4 mg of folic acid a day before and during early pregnancy prevented the recurrence of neural tube defects\textsuperscript{69}.

<table>
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<tr>
<th>Level</th>
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<tbody>
<tr>
<td>Folic acid supplements may be more effective than increased dietary folic acid intake\textsuperscript{72}</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 62 women showed that compared with folic acid supplements and fortified foods, consumption of extra folic acid-containing natural food was relatively ineffective at increasing folic acid status\textsuperscript{72}. The researchers concluded that the advice to women to consume folic acid-rich foods as a means to optimizes folic acid status is misleading\textsuperscript{72}.

### Deficiency

<table>
<thead>
<tr>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Low folic acid levels may be a risk factor for Down syndrome\textsuperscript{73}</td>
</tr>
</tbody>
</table>

A cohort study of 31 women with pregnancies affected by Down syndrome and of 60 age-matched controls showed that plasma levels of homocysteine were significantly increased in Down syndrome mothers and that serum levels of folic acid were significantly decreased in Down syndrome mothers\textsuperscript{73}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated homocysteine levels associated with recurrent spontaneous miscarriages\textsuperscript{74}</td>
</tr>
<tr>
<td>Reduces plasma homocysteine levels\textsuperscript{75}</td>
</tr>
</tbody>
</table>
A cohort study of 40 women with unexplained fetal loss showed an association with elevated serum homocysteine levels\textsuperscript{74}. Homocysteine levels can be safely reduced with folic acid, vitamin B6 and vitamin B12\textsuperscript{74-76}.

<table>
<thead>
<tr>
<th>Elevated homocysteine levels associated with placental abruption or infarction\textsuperscript{77}</th>
<th>1b</th>
</tr>
</thead>
</table>

A cohort study of 84 women with placental abruption or infarction and of 46 women with normal pregnancy outcome showed elevated homocysteine levels were associated with placental abruption or infarction\textsuperscript{77}. Homocysteine levels can be safely reduced with folic acid, vitamin B6 and vitamin B12\textsuperscript{74-76}.

**LACTATION**

<table>
<thead>
<tr>
<th>Folic acid levels can be depleted in the mother during lactation\textsuperscript{78}</th>
<th>1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk folic acid levels may decline post-partum\textsuperscript{78}</td>
<td>1a</td>
</tr>
<tr>
<td>Plasma homocysteine levels may increase post-partum in women no supplemented with folic acid\textsuperscript{78}</td>
<td>1a</td>
</tr>
</tbody>
</table>

A double-blind, randomized, longitudinal study of 42 lactating women found that a dietary folate intake of approximately 380 mcg daily may not be sufficient to prevent mobilization of maternal folate stores during lactation\textsuperscript{78}. In women not supplemented with folic acid, breast milk folic acid decreased and plasma homocysteine increased\textsuperscript{78}.

<table>
<thead>
<tr>
<th>300 mcg daily of folic acid may prevent folic acid decline in adolescent pregnancies\textsuperscript{79}</th>
<th>1a</th>
</tr>
</thead>
</table>
A randomized controlled trial of 71 breast-feeding adolescents (14 to 19 years) showed that 300 mcg daily of folic acid was sufficient to prevent a post-partum decline in folic acid\textsuperscript{79}.

**VITAMIN B6**

**PREGNANCY**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces dental decay during pregnancy\textsuperscript{80}</td>
<td>1a</td>
</tr>
</tbody>
</table>

A systematic review on the effects of vitamin B6 supplementation during pregnancy and labour found that vitamin B6 supplementation was associated with decreased incidence of dental decay in pregnant women\textsuperscript{80}.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces nausea and vomiting of pregnancy\textsuperscript{81, 82}</td>
<td>1a</td>
</tr>
<tr>
<td>Reduces nausea and vomiting of pregnancy (with ginger)\textsuperscript{83}</td>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 59 pregnant women found that 25 mg of vitamin B6 taken orally every 8 hours for 72 hours was effective in reducing the nausea and vomiting of pregnancy\textsuperscript{81}. Another randomized controlled trial of 342 pregnant women receiving 30 mg per day of vitamin B6 found that vitamin B6 was effective in reducing the severity of nausea during pregnancy\textsuperscript{82}.

A randomized controlled trial of 138 pregnant women found that vitamin B6 given in combination with ginger was effective in reducing nausea and vomiting during pregnancy\textsuperscript{83}.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-teratogenic\textsuperscript{84}</td>
<td>1b</td>
</tr>
<tr>
<td>Reduces congenital cardiovascular malformations\textsuperscript{84}</td>
<td>1b</td>
</tr>
</tbody>
</table>

A cohort study was conducted on 22,843 pregnant women with newborns or fetuses with congenital abnormalities and 38,151 matched controls of pregnant women who had newborn
infants without any congenital abnormalities. Treatment with vitamin B6 during pregnancy was found to be of non-teratogenic risk to the fetus, but may provide some protective effect for cardiovascular malformations.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves oxygenation of newborn at delivery</td>
</tr>
</tbody>
</table>

A loading dose of vitamin B6 (intramuscularly or per os) improved oxygen transport function of the newborn's blood when given to 24 non-supplemented pregnant women at term.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High doses may cause neonatal seizures</td>
</tr>
</tbody>
</table>

There is some concern that high-dose maternal vitamin B6 can cause neonatal seizures. There have been anecdotal reports of neonatal seizures after use of vitamin B6 by the mother for hyperemesis. High-dose vitamin B6 has also been shown to have a proconvulsant effect in mice and rats.

**Deficiency**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency of vitamin B6 may lead to slow growth in exclusively breastfed infants</td>
</tr>
</tbody>
</table>

An outcome study of 44 infants who were exclusively breastfed for 6 months showed that low vitamin B6 status was associated with reduced gain in length.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated homocysteine levels associated with recurrent spontaneous miscarriages</td>
</tr>
</tbody>
</table>
A cohort study of 40 women with unexplained fetal loss showed an association with elevated serum homocysteine levels\textsuperscript{74}. Homocysteine levels can be safely reduced with folic acid, vitamin B6 and vitamin B12\textsuperscript{74-76}.

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated homocysteine levels associated with placental abruption or infarction\textsuperscript{77}</td>
<td>1b</td>
</tr>
</tbody>
</table>

A cohort study of 84 women with placental abruption or infarction and of 46 women with normal pregnancy outcome showed elevated homocysteine levels were associated with placental abruption or infarction\textsuperscript{77}. Homocysteine levels can be safely reduced with folic acid, vitamin B6 and vitamin B12\textsuperscript{74-76}.

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency may be associated with oral lesions\textsuperscript{94}</td>
<td>1b</td>
</tr>
</tbody>
</table>

A comparative study of two groups of pregnant women of low socioeconomic status found an association between oral lesions and vitamin B6 deficiency during pregnancy\textsuperscript{94}.

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency may be associated with lower APGAR scores\textsuperscript{95}</td>
<td>1b</td>
</tr>
</tbody>
</table>

A cohort study of 127 low-income pregnant adolescent and adult women found lower APGAR scores in infants whose mothers were vitamin B6 deficient than those with adequate vitamin B6 status\textsuperscript{95}.

**LACTATION**

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk\textsuperscript{96}</td>
<td>1b</td>
</tr>
</tbody>
</table>
A cohort study of 47 healthy full-term infants found that maternal supplementation of 2.5 mg/day of vitamin B6 provided an adequate amount of vitamin B6 in breast milk for the growth of breast-fed infants\textsuperscript{96}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive breast-feeding without vitamin B6 supplementation may lead to deficiency after 6 months\textsuperscript{97}</td>
</tr>
</tbody>
</table>

On cohort study of 118 nursing women found that by 6 months of exclusive breast-feeding, 30% of cases of low vitamin B6 status in nursing mothers were reflected in their infants\textsuperscript{97}. The study concluded that for some infants, human milk alone, without supplementary foods, may be insufficient to meet vitamin B6 needs after 6 months of age\textsuperscript{97}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not interfere with breast milk production\textsuperscript{98,99}</td>
</tr>
<tr>
<td>May suppress plasma prolactin\textsuperscript{98}</td>
</tr>
</tbody>
</table>

An outcome study of 20 lactating women showed that although vitamin B6 may suppress plasma prolactin, vitamin B6 supplementation did not interfere with breast milk production\textsuperscript{98}. An observational study of 11 full-term infants found that supplemental B6 during pregnancy in ordinary doses does not have an anti-lactogenic effect\textsuperscript{99}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6 crosses into breast milk\textsuperscript{99}</td>
</tr>
</tbody>
</table>

An observational study of 11 full-term infants found that vitamin B6 was transported into breast milk\textsuperscript{99}.

References


Chapter 6 SUPPLEMENTS

The use of supplements is fairly widespread among the general public. Over-the-counter use of supplements is most common for joint support (arthritis and arthalgia), depression, insomnia, seasonal allergies and so on.

In this section, we selected 10 supplements are more commonly used by the general public. Our assumption is that given their frequency of use, pregnant and lactating mothers would likely continue administrating these supplements throughout gestation and lactation.

Each of the 10 supplement monographs are outlined as follows:

**Supplement name**

The name of the supplement, e.g. glucosamine sulfate.

**Description**

A brief description of the supplement, where it is derived from and what type of constituent it is (oil, amino acid, flavonoid).

**Main indication**

The main therapeutic indications for this herb. According to evidence-based medicines principles, the indications for this herb are evaluated based on grades of evidence (see methodology section).

**Pregnancy**

The safety of this herb during pregnancy. According to evidence-based medicines principles, the safety of this herb during pregnancy is evaluated based on grades of evidence (see Methodology section).
Lactation

The safety of this herb during lactation. According to evidence-based medicines principles, the safety of this herb during lactation is evaluated based on grades of evidence (see Methodology section).

**METHYL-SULFONYL-METHANE (MSM)**

MSM is a natural-occurring compound found in plants, algae and human milk\(^1\), MSM is an odorless metabolite of dimethyl sulfoxide (DMSO) and a source of sulfur for cysteine and methionine\(^2\).

**Main indications**

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayfever(^1)</td>
<td>C</td>
</tr>
<tr>
<td>Joint disorders(*)</td>
<td>E</td>
</tr>
</tbody>
</table>

\*(MSM is frequently used in the treatment of joint disorders and is often used in combination with glucosamine sulfate. Preliminary research shows that MSM inhibits degenerative changes in arthritic joints\(^3\).*

**Pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

Although the safety of MSM during pregnancy is unknown, it should be noted that there were no reports in the evidence-based medicine literature of MSM supplementation associated with abortion, teratogenicity, mutagenicity, uterine stimulation, menstrual stimulation (emmenagogue) or hormonal (estrogen, progesterone) activity.
**Lactation**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Although the safety of MSM is unknown during lactation, it should be noted that there are no reports in the evidence-based medicine literature of MSM supplementation associated with decreased lactation, hormonal activity or mutagenicity.

**GLUCOSAMINE SULPHATE**

Glucosamine sulfate is an amino sugar with a sulfate group attached. Glucosamine sulfate is a constituent of cartilage proteoglycans and can be synthetically derived or derived from marine exoskeletons.

**Main indications**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee osteoarthritis</td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
</tbody>
</table>

**Pregnancy**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

A natural products evidence-based database reported that glucosamine sulfate should be avoided in pregnancy and in women wishing to become pregnant. The database does not provide an explanation for this caution.
Although the safety of glucosamine during pregnancy is unknown, it should be noted that there were no reports in the evidence-based medicine literature of glucosamine supplementation associated with abortion, teratogenicity, mutagenicity, uterine stimulation, menstrual stimulation (emmenagogue) or hormonal (estrogen, progesterone) activity.

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use with caution in gestational diabetes</td>
<td>4</td>
</tr>
<tr>
<td>Does not affect type 2 diabetes mellitus$^9$</td>
<td>1a</td>
</tr>
<tr>
<td>Does not affect insulin sensitivitity$^9$</td>
<td>1a</td>
</tr>
</tbody>
</table>

Although the research indicates that glucosamine does not affect blood sugar metabolism in type 2 diabetics and does not affect insulin sensitivity, it should be used with caution until more is known of its effects during gestational diabetes.

A randomized controlled trial of type 2 diabetics demonstrated that oral glucosamine sulfate supplementation does not result in clinically significant alterations in glucose metabolism$^9$. A randomized controlled trial on 18 healthy subjects showed that glucosamine supplementation did not affect the regulation of insulin sensitivity in humans$^9$.

**Lactation**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake by mammary glands$^{10}$</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

Intravenous infusion of glucosamine through the jugular vein of a lactating cow lead to the isolation of lactosamine$^{10}$. The researchers concluded that these results showed the uptake of glucosamine in bovine mammary gland, and also indicated that a part of glucosamine was metabolized to the product lactosamine$^{10}$. No adverse effects were reported with respect to glucosamine administration$^{10}$.
Despite this study, there are no reports in the evidence-based medicine literature of glucosamine supplementation being either safe or contraindicated during lactation. As such, the safety of glucosamine sulfate during lactation is unknown

**QUERCETIN**

Quercetin is a dietary bioflavonoid found in many plants\(^a\).  

**Main indications**

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatitis(^\text{11})</td>
<td>B2</td>
</tr>
<tr>
<td>Hayfever*</td>
<td>E</td>
</tr>
</tbody>
</table>

* Quercetin is frequently used in the treatment of seasonal allergies. In vitro studies have shown that quercetin can inhibit histamine release from nasal scrapings by 46% to 96%\(^\text{12}\).

**Pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine relaxant(^\text{13})</td>
<td>3</td>
</tr>
</tbody>
</table>

In the rat uterus, quercetin was shown to relax the tonic contractions induced by potassium chloride\(^\text{13}\).

<table>
<thead>
<tr>
<th></th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-estrogenic activity(^\text{14-16})</td>
<td>3</td>
</tr>
</tbody>
</table>

Quercetin was shown have anti-estrogenic activity where it inhibited growth in cultures of breast cancer cells\(^\text{14}\). Quercetin was also shown to act as a potent inhibitor of estrone sulfatase *in vitro* and thus has the potential to express anti-estrogenic activity *in vivo* by decreasing estrogenic production in human liver cells\(^\text{15}\).
Doses of up to 2000 mg/kg of quercetin were administered to pregnant rats on the morning of day 9 of gestation\textsuperscript{17}. On day 20 of gestation, some quercetin-treated groups showed a significant decrease in the average weight of the fetuses compared with the corresponding control weight\textsuperscript{17}. The fetuses recovered on day 20 of gestation and failed to reveal any reproducible dose-related syndrome of teratogenic effects attributable to quercetin treatment\textsuperscript{17}.

Quercetin was shown to enhance the survival of purified rat spinal embryonic motoneurones after they have been sampled\textsuperscript{18}.

Quercetin was shown to inhibit the enzyme Ca(2+) activated ATPase in the mouse chorioallantoic placenta, thereby affecting transplacental calcium transport during mouse embryonic development\textsuperscript{19}.

At doses of up to 400 mg/kg, quercetin did not induce any post-implantation losses in mice and rats, thereby a reliable measure of non-lethal mutagnic activity\textsuperscript{20}. In male mice, however, there

<table>
<thead>
<tr>
<th>Level</th>
<th>Non-teratogenic\textsuperscript{17}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>May lower fetus body weight\textsuperscript{17}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Non-embryotoxic\textsuperscript{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>May interfere with transplacental calcium transport\textsuperscript{19}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Non-mutagenic\textsuperscript{20}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>May cause infertility in males (inconclusive)\textsuperscript{20}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
was a profound reduction in fertility at 300 and 400 mg/kg of quercetin; this relationship was not observed in male rats\(^{20}\). The researchers hypothesized that the loss of fertility could be due to germinal cytotoxicity, oligospermia or impairment of fertilizing ability by quercetin\(^{20}\).

<table>
<thead>
<tr>
<th>Level</th>
<th>May interfere with tissue proliferation in the uterus(^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

In rats, quercetin was shown to interfere with a protein kinase enzyme responsible for tissue proliferation in the uterus\(^{21}\). **Lactation**

<table>
<thead>
<tr>
<th>Level</th>
<th>Blocks binding of prolactin(^{22})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Quercitin was shown to block prolactin action on milk protein genes in the mammary gland\(^{22}\).

<table>
<thead>
<tr>
<th>Level</th>
<th>May interfere with growth of mammary gland cells(^{21,23})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Quercitin was shown to inhibit the activity of a protein kinase enzyme responsible for the growth of mammary gland cells in lactating mice\(^{21,23}\).

**5-HYDROXYTRYPTOPHAN (5-HTP)**

5-HTP is an amino acid that readily crosses the blood-brain barrier and increases central nervous system (CNS) synthesis of serotonin\(^{24}\).

**Main indications**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Depression(^{24})</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>Fibromyalgia(^{25})</td>
</tr>
</tbody>
</table>
### Pregnancy

<table>
<thead>
<tr>
<th>Level</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Increases serum levels of prolactin&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Oral administration of 5-HTP in 10 obese but otherwise healthy women was shown to increase serum levels of prolactin<sup>26</sup>. During pregnancy and lactation, prolactin levels normally increase<sup>27</sup>. High levels of prolactin, as in the case of hyperprolactinemia, may be associated with reproductive dysfunctions due to menstrual irregularities and amenorrhea<sup>28</sup>.

<table>
<thead>
<tr>
<th>Level</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>May contain impurities associated with eosinophilia-myalgia syndrome&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

The United States Food and Drug Administration (FDA) reported that an impurity known as “Peak X” was identified in dietary supplements containing 5-HTP<sup>29</sup>. In 1991, one case of eosinophilia-myalgia syndrome (EMS) was associated with 5-HTP<sup>29</sup>. EMS is a serious systemic illness characterized by elevations of certain white blood cells and severe muscle pain<sup>29</sup>.

<table>
<thead>
<tr>
<th>Level</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Increases fetal breathing movement&lt;sup&gt;30, 31&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

5-HTP was shown to prolong high-voltage electrocortical activity and increase the incidence of fetal breathing movements in animals<sup>30, 31</sup>.

<table>
<thead>
<tr>
<th>Level</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Although the safety of 5-HTP during pregnancy is unknown, it should be noted that there were no reports in the evidence-based medicine literature of 5-HTP supplementation associated with abortion, teratogenicity, mutagenicity, uterine stimulation, menstrual stimulation (emmenagogue) or hormonal (estrogen, progesterone) activity.
Lactation

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Increases serum levels of prolactin\(^{26}\) | 1b  

Oral administration of 5-HTP in 10 obese but otherwise healthy women was shown to increase serum levels of prolactin\(^{26}\). During pregnancy and lactation, prolactin levels normally increase\(^{27}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Unknown | 5  

There are no reports in the evidence-based medicine literature of 5-HTP supplementation being either safe or contraindicated during lactation.

**COENZYME Q10 (CO Q10)**

Coenzyme Q-10 is fat soluble and a vitamin-like compound that is present in all cells and membranes and in addition to being a member of the mitochondrial respiratory chain\(^{32}\).

**Main indications**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
</table>
| Congestive heart failure\(^{33-35}\) | A  
| Hypertension\(^{36,37}\) | B2  

**Pregnancy**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
</table>
| Unknown | 5  

Although the safety of CoQ10 during pregnancy is unknown, it should be noted that there were no reports in the evidence-based medicine literature of CoQ10 supplementation associated with
abortion, teratogenicity, mutagenicity, uterine stimulation, menstrual stimulation (emmenagogue) or hormonal (estrogen, progesterone) activity.

**Blood Levels**

<table>
<thead>
<tr>
<th>Level</th>
<th>Low serum levels associated with abortion$^{38}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td></td>
</tr>
</tbody>
</table>

A cohort study of 483 pregnancies found that low levels of CoQ10 in maternal blood were observed in spontaneous abortions, in threatened late abortions and in threatened pre-term deliveries$^{38}$. The authors concluded that CoQ10 was a marker of pathological uterine contractile activity$^{38}$.

<table>
<thead>
<tr>
<th>Level</th>
<th>Low serum levels associated with preeclampsia$^{39,40}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td></td>
</tr>
</tbody>
</table>

Two cohort study showed that during preeclampsia, there is a significant decrease in plasma levels of coenzyme Q10 compared to normal pregnant women$^{39,40}$.

**Lactation**

<table>
<thead>
<tr>
<th>Level</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

There are no reports in the evidence-based medicine literature of CoQ10 supplementation being either safe or contraindicated during lactation.

**BROMELAIN**

Bromelain is a natural proteinase preparation derived from the stem of the pineapple$^{41}$.
Main indications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Breast engorgement during lactation (with trypsin)(^42)</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Knee osteoarthritis(^{43,44})</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Ankylosing spondylitis(^{45})</td>
<td>C</td>
</tr>
</tbody>
</table>

Pregnancy

<table>
<thead>
<tr>
<th>Level</th>
<th>Bromelain</th>
<th>Unknown 5</th>
</tr>
</thead>
</table>

Although the safety of bromelain during pregnancy is unknown, it should be noted that there were no reports in the evidence-based medicine literature of bromelain supplementation associated with abortion, teratogenicity, mutagenicity, uterine stimulation, menstrual stimulation (emmenagogue) or hormonal (estrogen, progesterone) activity.

<table>
<thead>
<tr>
<th>Pineapple</th>
<th>Emmenagogue(^{46}) 4</th>
<th>Potential abortifacient(^{46}) 4</th>
<th>Estrogenic(^{47})</th>
</tr>
</thead>
</table>

With respect to pineapple, however, a review article on the potential value of plants as sources of anti-fertility agents reported that the leaf, fruit and juice of pineapple were emmenagogues and potential abortifaciens, and that they had estrogenic activity\(^{46,47}\).
Intravaginal use

<table>
<thead>
<tr>
<th>May dilate cervical canal\textsuperscript{48}</th>
<th>1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid intravaginal use\textsuperscript{49,50}</td>
<td>1c</td>
</tr>
</tbody>
</table>

Through radiographic observation, intravaginal use of bromelain was shown to dilate and widen the cervical canal and to soften the cervix\textsuperscript{48}. Two studies reported that the mucolytic activity of bromelain could be useful in cleaning the mucus plug in the cervical os in order to get better radiographs during cervicohysterograms\textsuperscript{49,50}. Although not stated by the researchers, dilation of the cervix and dissolution of the cervical plug when bromelain is used intravaginally may adversely affect pregnancy outcome.

**Lactation**

| Minimal risk\textsuperscript{42} | 1a |

A systematic review was conducted on the efficacy of various treatments to relieve symptoms of breast engorgement among breastfeeding women\textsuperscript{42}. In combination with trypsin, bromelain was shown to significantly improved symptoms of breast engorgement\textsuperscript{42}. No adverse effects were reported with respect to taking bromelain during lactation\textsuperscript{42}.

**FISH OILS**

**Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (EPA)**

Eicosapentaenoic acid (EPA) and DHA are long-chain n-3 polyunsaturated fatty acids that are found in the tissues of marine mammals and oily fish\textsuperscript{4}. 
Main indications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hyperlipedemia$^{51,52}$</th>
<th>Heart disease prevention$^{53}$</th>
<th>Hypertension$^{54}$</th>
</tr>
</thead>
</table>

Pregnancy

<table>
<thead>
<tr>
<th>Level</th>
<th>Minimal risk$^{55-58}$</th>
</tr>
</thead>
</table>

A double-blind randomized controlled study of 590 pregnant women (19-35 years old) in weeks 17 to 19 of pregnancy showed no harmful effects of maternal supplementation with fish oils regarding pregnancy outcome, cognitive development, or growth$^{58}$.

| Level | Longer gestational length$^{58}$ | Increased cerebral maturation$^{58}$ |

Neonates with a high concentration of DHA in umbilical plasma had longer gestational length and mature EEG on the second day of life than neonates with low concentration$^{58}$.

| Level | Improves postnatal oxidative stress$^{59}$ | May reduce expression of allergic disease$^{59}$ |

A randomized controlled trial of 83 pregnant atopic women showed that maternal supplementation with fish oil can attenuate neonatal lipid peroxidation, reduce postnatal oxidative stress and reduce expression of allergic disease$^{59}$.
<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves mental processing and IQ\textsuperscript{60}</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 341 mothers showed that children who were born to mothers who had taken cod liver oil during pregnancy and lactation scored higher on the Mental Processing Composite at 4 years of age as compared with children whose mothers had taken corn oil\textsuperscript{60}. The children's mental processing scores at 4 years of age correlated significantly with maternal intake of DHA and EPA during pregnancy\textsuperscript{60}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levels in the mother correlate to newborn levels\textsuperscript{55-57}</td>
</tr>
</tbody>
</table>

A cross-sectional study of 162 mothers found that omega-3 fatty acid intake by the mother was directly correlated to levels in the newborn\textsuperscript{55}. An outcome study of 23 healthy pregnant women found that children born to mothers supplemented with fish oil in the last trimester of pregnancy start with a better DHA status at birth, which may be beneficial to neonatal neurodevelopment\textsuperscript{56}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-toxic\textsuperscript{61,62}</td>
</tr>
<tr>
<td>Non-genotoxic\textsuperscript{61}</td>
</tr>
<tr>
<td>Anti-mutagenic\textsuperscript{63}</td>
</tr>
</tbody>
</table>

DHA produced negative results in genotoxicity assays and demonstrated a low acute oral toxicity in mice and rats\textsuperscript{61}. EPA and DHA were shown to have anti-mutagenic activity in Chinese hamster cells\textsuperscript{63}. EPA and DHA were shown to have low toxicity in human leukemic cell lines\textsuperscript{62}. 
Fish may contain contaminants such as methylmercury, dioxins and polychlorinated biphenyls (PCBs), that are harmful to pregnant and nursing mothers\(^{64}\). Although these safety concerns apply principally to fish meat, ensure that fish oil supplements do not contain methylmercury, dioxins, PCBs and any other contaminants. Verify with manufacturer that there are laboratory reports indicating the absence of contaminants in their fish oil product.

### Lactation

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^{58})</td>
</tr>
</tbody>
</table>

A double-blind randomized controlled study of 590 pregnant women (19-35 years old) in weeks 17 to 19 of pregnancy showed that supplementation with fish oil did not adversely affect lactation\(^{58}\).

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevates milk DHA content(^{58,66})</td>
</tr>
</tbody>
</table>

A double-blind randomized controlled study of 590 pregnant women (19-35 years old) in weeks 17 to 19 of pregnancy showed that breast milk of mothers supplemented with cod liver oil contained more omega-3 fatty acids than breast milk of mothers supplemented with corn oil\(^{58}\). A study of 8 lactating women showed that dietary intake of fish oil significantly elevated milk DHA content, which would elevate the newborn’s DHA intake\(^{66}\). DHA is essential for brain, nervous tissue and retinal development during the 1st year of life\(^{66}\).
A randomized controlled trial of 56 newborns showed that early dietary supply of DHA was a major dietary determinant of improved performance on mental development indexes. A randomized controlled trial of 341 mothers showed that children who were born to mothers who had taken cod liver oil during pregnancy and lactation scored higher on the Mental Processing Composite at 4 years of age as compared with children whose mothers had taken corn oil.

A randomized controlled trial of 180 newborns showed that dietary DHA and arachidonic acid supplementation improved visual acuity development.

In a randomized controlled trial of 83 pregnant women, supplementation with fish oil during pregnancy significantly altered early post-partum breast milk fatty acid composition. Omega-3 fatty acid levels were positively associated with IgA and sCD14 levels, suggesting a relationship between fatty acid status and mucosal immune function.

Blood samples of preterm infants showed that a too-high supply of EPA in addition to DHA might be harmful to mental development.
Fish

| Potential contamination\(^{64, 65}\) | 4 |

Fish may contain contaminants such as methylmercury, dioxins and polychlorinated biphenyls (PCBs), that are harmful to pregnant and nursing mothers\(^{64}\). Although these safety concerns apply principally to fish meat, ensure that fish oil supplements do not contain methylmercury, dioxins, PCBs and any other contaminants. Verify with manufacturer that there are laboratory reports indicating the absence of contaminants in their fish oil product.

**SOY ISOFLAVONES**

Soy isoflavones are heterocyclic phenols that are structurally similar to estradiol and to selective estrogen-receptor modulators (SERM)\(^4\). Soy isoflavones contain the isoflavone glucosides genistein and daidzein in their inactive conjugated forms\(^4\).

**Main indications**

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia(^{71-73})</td>
</tr>
<tr>
<td>Menopausal symptoms(^{72, 74})</td>
</tr>
<tr>
<td>Breast cancer prevention(^{75, 76})</td>
</tr>
</tbody>
</table>

**Pregnancy**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak estrogenic activity(^{77, 78})</td>
</tr>
<tr>
<td>Increases sex hormone binding globulin (SHBG)(^{79})</td>
</tr>
</tbody>
</table>
A study on 18 post-menopausal women found that soy supplementation did not exert clinically important estrogenic effects on vaginal epithelium or endometrium77. Another study of 84 pre-menopausal women found short term dietary soy has a weak estrogenic response on the breast78. A study on 20 postmenopausal women found that soy consumption significantly increased SHBG in subjects whose SHBG concentrations are in the low end of the concentration range79.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential allergen80</td>
</tr>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 288 pregnant women showed that a hypoallergenic diet, excluding allergens such as soy, during the 3rd trimester of pregnancy and during lactation reduce food sensitization and allergy during the first year of life80.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of hypospadias81</td>
</tr>
<tr>
<td>1b</td>
</tr>
</tbody>
</table>

A prospective cohort study of 7,928 boys born to mothers taking part in the Avon Longitudinal Study of Pregnancy and Childhood found that mothers who were vegetarian in pregnancy had higher odds of giving birth to a boy with hypospadias81. The researchers concluded that these results support the possibility that phytoestrogens, such as soy and soy milk, may have a deleterious effect on the developing male reproductive system81.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflicting evidence</td>
</tr>
<tr>
<td>May affect sexual development82-85</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Gestational and lactational exposure to genistein resulted in temporary, prepubertal urogenital abnormalities in male rats83. Males exposed to genistein had smaller anogenital distance and testis size, and delayed preputial separation83. Gestation and lactation exposure to genistein also caused long-term dysfunction in reproductive behaviour, in which adult males exposed to genistein were less likely to mount, intromit and ejaculate during mating tests83. Males exposed to genistein also had lower testosterone concentrations in adulthood83.
In 2 other studies, gestational and lactational exposure of mice to genistein at human exposure levels did not induce adverse effects on sperm quality, changes in testicular gene expression or any adverse effects on the reproductive organs in mice at the human intake dose level\textsuperscript{84, 85}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces body weight\textsuperscript{86}</td>
</tr>
<tr>
<td>Does not affect endocrine function\textsuperscript{86}</td>
</tr>
</tbody>
</table>

In rats, genistein supplementation was shown to reduced body weight at week 11, but not to affect endocrine parameters\textsuperscript{86}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses the placenta\textsuperscript{87}</td>
</tr>
</tbody>
</table>

In a study of human amniotic fluid following phytoestrogen ingestion, dietary phytoestrogens were quantified in 96.2\% of second trimester amniotic fluid samples tested\textsuperscript{87}. Second trimester amniotic fluid contained quantifiable levels of dietary phytoestrogens, including daidzein, genistein, formononetin, biochanin A, and coumestrol\textsuperscript{87}.

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May affect progesterone receptor\textsuperscript{88}</td>
</tr>
</tbody>
</table>

Genistein was found to increase progesterone receptor (PR) in the uterine glandular epithelium, where PR is essential for regulating key female reproductive processes, such as uterine proliferation, implantation, and maintenance of pregnancy\textsuperscript{88}. Increased PR expression suggests that genistein exposure during reproductive development may have long-term reproductive health consequences\textsuperscript{88}.
<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflicting evidence</td>
</tr>
<tr>
<td>May increase or have a protective effect on mammary tumours&lt;sup&gt;89, 90&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Subcutaneous exposure to genistein, mimicking the effects of in utero estrogenic exposures, dose-dependently increased the incidence mammary tumors in rats, when compared with the controls<sup>89</sup>. However, another study showed that administration of genistein in the perinatal period had protective effects against induced mammary carcinoma in rats<sup>90</sup>.

**Food amounts**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;91&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

According to the United States Food and Drug Administration (FDA), soy consumption in foods amounts presents minimal risk during pregnancy<sup>91</sup>.

**Lactation**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflicting evidence – may affect sexual development&lt;sup&gt;82-85&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Gestational and lactational exposure to genistein resulted in temporary, prepubertal urogenital abnormalities in male rats<sup>83</sup>. Males exposed to genistein had smaller anogenital distance and testis size, and delayed preputial separation<sup>83</sup>. Gestation and lactation exposure to genistein also caused long-term dysfunction in reproductive behaviour, in which adult males exposed to genistein were less likely to mount, intromit and ejaculate during mating tests<sup>83</sup>. Males exposed to genistein also had lower testosterone concentrations in adulthood<sup>83</sup>. 
In 2 other studies, gestational and lactational exposure of mice to genistein at human exposure levels did not induce adverse effects on sperm quality, changes in testicular gene expression or any adverse effects on the reproductive organs in mice at the human intake dose level\textsuperscript{84, 85}.

| Level |  
|---|---
| Conflicting evidence – may or may not affect morphological changes in mammary glands\textsuperscript{82, 92} | 3 |

In one study, postnatal exposure to pharmacological levels of genistein induced profound morphological changes in the mammary glands of adult female rats, reflecting estrogenic activity\textsuperscript{92}. In another study, \textit{in utero} and lactational exposure to genistein at levels comparable to or greater than human exposures did not adversely affect mammary gland development in pubertal female mice\textsuperscript{82}.

Food amounts

| Level |  
|---|---
| Minimal risk\textsuperscript{91} | 4 |

According to the United States Food and Drug Administration (FDA), soy consumption in foods amounts presents minimal risk during lactation\textsuperscript{91}.

\textbf{LACTOBACILLUS SP.}

Lactobacillus refers to a group of lactic acid producing, gram-positive rods that are obligate and facultative anaerobes\textsuperscript{93}. Lactobacillus species include \textit{Lactobacillus acidophilus}, \textit{Lactobacillus bulgaricus}, \textit{Lactobacillus casei}, \textit{rhamnosus}, \textit{Lactobacillus delbrueckii}, \textit{Lactobacillus fermentum}, \textit{Lactobacillus plantarum}, \textit{Lactobacillus reuteri}, \textit{Lactobacillus rhamnosus}, and \textit{Lactobacillus sporogenes}\textsuperscript{4}. 
## Main indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea&lt;sup&gt;94, 95&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Atopic disease&lt;sup&gt;96, 97&lt;/sup&gt;</td>
<td>B1</td>
</tr>
</tbody>
</table>

### Pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk&lt;sup&gt;98&lt;/sup&gt;</td>
<td>1b</td>
</tr>
<tr>
<td>May reduce the risk of preterm delivery&lt;sup&gt;99&lt;/sup&gt;</td>
<td>1b</td>
</tr>
<tr>
<td>Mother-to-newborn infant transmission&lt;sup&gt;100, 101&lt;/sup&gt;</td>
<td>1c</td>
</tr>
</tbody>
</table>

A total of 32 women with bacterial vaginosis in the first trimester of pregnancy were treated with intravaginal application of yogurt, which contains *Lactobacillus sp.*<sup>98</sup>. The yogurt treatment restored the normal acidity and vaginal flora, without systemic effect to the mother or fetus<sup>98</sup>.

A prospective study of the vaginal flora in the second trimester was undertaken in 1958 women with singleton pregnancies<sup>99</sup>. Absence of Lactobacilli was identified as an independent risk factor and as a predictor for preterm delivery at < 33 weeks of gestation<sup>99</sup>. The study suggests that tests for determining the presence of vaginal lactobacilli may be clinically useful tools for identifying women at an increased risk of preterm delivery at < 33 weeks of gestation<sup>99</sup>.

A study of 86 pregnant women tested for vaginal lactobacilli showed that approximately one-fourth of infants acquire vaginal lactobacilli from their mothers at birth, and that the acquired lactobacilli do not last in the intestine of the infant long-term, but rather, are replaced by ones from milk or unknown sources after birth<sup>101</sup>. Six children whose mothers supplemented with
*Lactobacillus GG* during pregnancy showed temporary colonization of the gastrointestinal tract for as long as 6 months post-delivery, and in some cases, as long as 24 months post-delivery\(^9\).

**Lactobacillus GG (L. rhamnosus)**

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^9,9)</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 62 mother-infant pairs showed that administering probiotics to pregnant and lactating mothers increased the immunoprotective potential of breast milk\(^9\). The researchers observed that administering probiotics during pregnancy and lactation was safe and effective\(^9\). Another randomized controlled trial was conducted on 132 mother-infant pairs where *Lactobacillus GG* was used with apparent safety during pregnancy\(^9\).

**Lactation**

Lactobacillus GG (L. rhamnosus)

<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk(^9,9)</td>
</tr>
</tbody>
</table>

A randomized controlled trial of 62 mother-infant pairs showed that administering probiotics to pregnant and lactating mothers increased the immunoprotective potential of breast milk\(^9\). The researchers observed that administering probiotics during pregnancy and lactation was safe and effective\(^9\). Another randomized controlled trial was conducted on 132 mother-infant pairs where *Lactobacillus GG* was used with apparent safety in lactating women for up to six months\(^9\).

**References**


93. Fujisawa T, Benno Y, Yaeshima T, Mitsuoka T. Taxonomic study of the Lactobacillus acidophilus group, with recognition of Lactobacillus gallinarum sp. nov. and Lactobacillus


Appendix B

Published manuscripts where student is not first or last author


SAFETY AND EFFICACY OF ECHINACEA (ECHINACEA AUGUSTAFOLIA, E. PURPUREA AND E. PALLIDA) DURING PREGNANCY AND LACTATION

Daniel Perri MD, BscPharm, FRCP(C) (2)
Jean-Jacques Dugoua ND, BSc (Hons.) (1,4)
Edward Mills DPH, MSc (1)
Gideon Koren MD (2,3)

1) Department of Clinical Epidemiology, Canadian College of Naturopathic Medicine
2) Department of Clinical Pharmacology and Toxicology, University of Toronto
3) Motherisk Program, Hospital for Sick Children
4) Artist Health Center, Toronto Western Hospital

Corresponding Author:
Edward Mills
Canadian College Of Naturopathic Medicine – Department of clinical epidemiology
1255 Sheppard Ave E.
Toronto, ON M2K 1E2
Tel: 416-498-1255 x324
Fax: 416-498-1643
e mills@ccnm.edu

Title: Safety and efficacy of Echinacea (Echinacea augustafolia, E. purpurea and E. pallida) during pregnancy and lactation.
Authors: Perri D, Dugoua JJ, Mills E, Koren G
Background: There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for common herbs used during pregnancy and lactation.
Objectives: To systematically review the literature for evidence on the use, safety, and pharmacology of Echinacea focusing on issues pertaining to pregnancy and lactation.
Methods: We searched 7 electronic databases and compiled data according to the grade of evidence found.
Results: We found varying levels of scientific evidence on efficacy of use for different conditions, strong evidence of safety during pregnancy and low-level evidence of safety during lactation.
Conclusions: Echinacea shows very strong scientific evidence of being an effective aid in the treatment of upper respiratory tract infections (URTI) and good evidence in the prevention of URTI. There is strong scientific evidence that oral consumption of Echinacea during the first trimester does not increase risk for major malformations. Although based on expert panel opinion, oral
consumption of Echinacea in recommended doses is reported as safe for use during pregnancy and lactation.

**Keywords:** Echinacea, *Echinacea augustifolia, Echinacea purpurea, Echinacea pallida*, pregnancy, lactation, breastfeeding, systematic review

**Introduction**
Echinacea is a perennial herb found in Eastern and Central United States and Southern Canada. While there are nine species of Echinacea, three are most commonly used as medicinal products – *Echinacea augustifolia, E. purpurea, and E. pallida*. Historically, Echinacea was the most commonly used herb amongst Native North Americans for a variety of conditions including wounds, insect bites, infections, toothache, joint pain, and as an antidote for rattlesnake bites. In the early 20th century it was established as the remedy of choice for cold and flu and was commonly used as an anti-infective until the advent of modern antibiotics. Its use in North America declined until the 1980s when consumer interest grew in immune stimulants for conditions such as AIDS, cancer, and chronic fatigue syndrome. Since then, it has made a resurgence as a remedy for viral infections including influenza and the common cold. Over the last decade it has consistently been one of the top selling herbal products in Canada and for several years has been one of the top three herbal products sold in the United States.

Each year over 6000 telephone calls are made to Motherisk (a teratology information center at the Hospital for Sick Children in Toronto) with regards to the safety of natural health products in pregnancy and lactation. A significant number of those calls pertain to the safety of echinacea. This is a trend common throughout North America as nearly one-sixth of American women took at least one herbal supplement in the year 2000. Even during pregnancy and lactation a significant number of women continue to use natural products. A recent Norwegian study found that 36% of women had used herbal drugs during pregnancy. The incidence of use increased throughout the first, second, and third trimester. Of those who used herbs, 39% were exposed to products either considered possibly harmful or with no known safety profile. While the use of herbal medicines during pregnancy is not as popular in Canada as it is in other parts of the world, this striking data demonstrates the need for health care personnel to have knowledge about the therapeutic effectiveness and safety of herbal products in pregnancy and lactation. To meet this knowledge void we have undertaken a systematic review of the literature as it pertains to the effectiveness of Echinacea as well as to its safety during pregnancy and lactation.

**Synonyms/Common Names/Related Substances**
American cone flower, black Sampson, black Susan, *Brauneria angustifolia, Brauneria pallida*, comb flower, coneflower, echinaceawurzel, hedgehog, igelkopfwurzel, Indian head, Kansas snakeroor, narrow-leaved purple cone flower, pale coneflower, purple cone flower, purpursonnenhutkraut, purpursonnenhutwurzel, racine d’echinacea, red sunflower, rock-up-hat, roter sonnenhut, schmallblaättrige kegelblumenwurzel, schmallblaättriger sonnenhut, scurvy root, snakeroor, sonnenhutwurzel
Constituents
Caffeic acid derivatives (echinocoside, cichoric acid, cynarin), polysaccharides, glycoproteins, alkamides

Parts used
Roots, stems and leaves

Methods
We searched the following databases from inception to June 2004: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as keywords along with “pregnancy”, “lactation” and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The grade of evidence for indications was evaluated as displayed in Table 1. We rated evidence of harm as displayed in Table 2.

Results

Indications for use

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection - Treatment</td>
<td>A</td>
</tr>
<tr>
<td>Upper respiratory tract infection - Prevention</td>
<td>B2</td>
</tr>
<tr>
<td>Radiation associated leukopenia</td>
<td>B2</td>
</tr>
<tr>
<td>Cancer survival time</td>
<td>C</td>
</tr>
</tbody>
</table>

Safety of consumption during pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not associated with an increased risk for major malformations</td>
<td>1b</td>
</tr>
</tbody>
</table>

A prospective follow-up study on 206 pregnant women, 112 of which had used Echinacea in the first trimester of pregnancy reported that gestational use of Echinacea during the first trimester (organogenesis) is not associated with an increased risk for major malformations. The German Commission E compendium, produced by an expert panel on botanical medicine, considers oral Echinacea in recommended doses safe for use during pregnancy.

Safety of consumption during lactation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe in recommended doses</td>
<td>4</td>
</tr>
</tbody>
</table>

The German Commission E compendium, produced by an expert panel on botanical medicine, considers oral Echinacea in recommended doses safe for use
during lactation. Echinacea was not reported in the evidence-based medicine literature as being either safe or contraindicated during lactation.

**Toxicity**
The LD$_{50}$ in mice is over 2500 mg/kg and the LD$_{50}$ of intravenous Echinacea juice is 50 mL/kg.

**Pharmacology**
The immune-stimulating properties have Echinacea have not been attributed to any single compound. Echinacea increases the proliferation of phagocytes in spleen and bone marrow, stimulates monocytes to produce cytokines (IL-1, IL-6, TNF), increases the number of PMN, activates macrophages and promotes the adherence of PMN to endothelial cells.

Echinacea has anti-viral, anti-bacterial and anti-fungal properties. Echinacea was shown to inhibit the influenza virus and the herpes simplex virus (I and II). Topically, Echinacea has anti-inflammatory properties where it inhibits edema. Echinacea may interfere with cytochrome P450 (CYP) 3A4 (CYP3A4) enzyme.

**Drug interactions**
Immunosuppressant drugs
Drugs metabolized by the cytochrome P450 (CYP) 3A4 (CYP3A4) enzyme

**Discussion**
There is very strong scientific evidence for the use of Echinacea in the treatment of upper respiratory tract infections. There is good scientific evidence for the use of Echinacea for the prevention of upper respiratory tract infections and for radiation associated leukopenia. There is also fair scientific evidence of Echinacea use in cancer survival time.

During pregnancy, strong scientific evidence via a prospective follow-up study found that oral consumption of Echinacea during the first trimester was not associated with an increased risk for major malformations. Further theoretical evidence via an expert panel on botanical medicine reported that oral consumption of Echinacea in recommended doses is safe for use during pregnancy.

Although an expert panel on botanical medicine reported that oral consumption of Echinacea in recommended doses is safe for use during lactation, Echinacea should be used with caution until there is stronger evidence of its safety.

While traditional and common use has not indicated any substantive risks of taking this herb during pregnancy and lactation, clearly more rigorous and well-controlled research is needed in this area. Clinicians and patients should also be concerned about the potential for interactions that may occur between Echinacea and immunosuppressant drugs.
**Table 1. Levels of evidence for efficacy**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<tr>
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<td>Evidence from case series.</td>
</tr>
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<td>E</td>
<td>INDIRECT AND/OR CLINICAL EVIDENCE</td>
</tr>
<tr>
<td></td>
<td>Evidence from case reports OR expert opinion OR laboratory studies.</td>
</tr>
<tr>
<td>F</td>
<td>HISTORICAL OR TRADITIONAL EVIDENCE</td>
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<tr>
<td></td>
<td>Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.</td>
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Table 2. Levels of evidence for harm

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</tr>
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<td>Evidence based on case reports.</td>
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<td>IN VITRO SCIENTIFIC EVIDENCE</td>
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<td>Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
</tr>
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<td>Evidence based on scientific theory OR expert opinion.</td>
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</tbody>
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REFERENCES

SAFETY AND EFFICACY OF PANAX GINSENG
DURING PREGNANCY AND LACTATION

Dugald Seely, ND (1,2)
Jean-Jacques Dugoua, HBSc ND PhD (cand.) (1,3,4)
Daniel Perri, MD, BscPharm, FRCP(C) (5)
Edward Mills, DPH, MSc, PhD (1,6)
Gideon Koren, MD (4,5)

5) Department of Research and Clinical Epidemiology, The Canadian College of Naturopathic Medicine
6) Institute of Medical Science, University of Toronto
7) Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto
8) Motherisk, Hospital for Sick Children, Toronto
9) Division of Clinical Pharmacology and Toxicology, University of Toronto
10) Clinical Epidemiology & Biostatistics, McMaster University

Word count: 1804

Tables: 3

Correspondence:

Jean-Jacques Dugoua
Leslie Dan Faculty of Pharmacy
University of Toronto
144 College Street
Toronto, Ontario, Canada M5S 3M2
Tel: (416) 813-5781
Fax: (416) 813-7562
jeanjacques.dugoua@utoronto.ca

Keywords: Panax Ginseng, Asian ginseng, ginseng, pregnancy, lactation, breastfeeding, systematic review
Abstract

Title: Safety and efficacy of Panax ginseng during pregnancy and lactation.

Authors: Seely D, Dugoua JJ, Perri D, Koren G, Mills E

Background: There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and the safety of herbs used by women during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

Objectives: To systematically review the literature for evidence on the use, safety and pharmacology of Panax ginseng with a particular focus on issues pertaining to pregnancy and lactation.

Methods: We searched 7 electronic databases from inception to June 2006 and compiled data according to the grade of evidence that was found.

Results: Based on strong scientific evidence from a cohort study, Panax ginseng was not associated with adverse effects when used during pregnancy. Panax ginseng was misreported in the literature as causing androgenization, when in fact the case reported was due to an adulterant. There is in vitro evidence of teratogenicity with exposure to ginsenosides; however, this evidence is derived from animal embryos and is based on exposure to isolated ginsenosides at much higher levels than achievable through normal consumption in humans. There is also conflicting evidence as to whether or not Panax ginseng has estrogenic properties. In lactation, there are no human studies on the safety of Panax ginseng, only in vitro evidence based on three animal studies reporting minimal risk.

Conclusions: Panax ginseng should be consumed with caution during pregnancy, especially during the first trimester, and during lactation.
Introduction

There are five main species of ginseng: American, Chinese, Korean, Japanese, and Siberian (or Russian) and it is important to be able to distinguish between them. The commercially available product ‘ginseng’ usually refers to the dried root of Panax ginseng, commonly known as Korean or Asian ginseng. Preparations of P. ginseng include the steam-dried root that is called ‘red ginseng’, and the air-dried root that is called ‘white ginseng’[1]. Fresh ginseng extract is also consumed but is not generally the preparation available commercially[2].

Panax ginseng is a popular herbal remedy that has been in use for thousands of years. It has been an important part of the pharmacopoeia of Traditional Chinese Medicine and is classified as an adaptogen that is thought to increase the body’s overall resistance to stress and infection[3]. This herb has a wide base of application and is considered the most popular herbal medicine worldwide[4]. It has been used to treat a variety of disorders including: anaemia, insomnia, dyspnea, memory impairment, confusion, decreased libido, chronic fatigue, angina, diabetes mellitus, and herpes simplex type-II infections[2, 5, 6].

P. ginseng is not considered an herb specific to women’s health issues, however its broad base of popularity will invariably involve its usage by women of reproductive age and women who may be potentially pregnant. We have conducted a systematic review of the literature to assess issues of efficacy, and potential safety for women who are pregnant, planning to become pregnant or those who are breast-feeding.

Synonyms/common names/related substances[7]

Asian ginseng, Asiatic ginseng, Chinese ginseng, ginseng, ginseng asiatique, Ginseng radix, ginseng root, guigai, hong shen, Japanese ginseng, jen-shen, jinsao, jintsam, insam, Korean
ginseng, Korean panax ginseng, Korean red ginseng, ninjin, Oriental ginseng, *Panax ginseng, Radix ginseng rubra*, red ginseng, ren shen, renshen, renxian, sang, seng, sheng shai shen, white ginseng

**Constituents:**

Triterpenoid Saponins: ginsenosides (Rg1, Rb1)
Polyacetylenic constituents[8]: panaxynol, panaxydol, panaxytriol

Panaxagin[9]

Essential oil[10]
Phytosterol[10]
Pectin[11]

B vitamins[11]
Flavonoids[11]

**Part used:**

Root and rhizomes [7]

**Methods**

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provide information as to the safety, efficacy and pharmacology of cranberry in pregnancy and lactation. Our search included the following databases from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and the Latin name of the herb were used as the key words along with “pregnancy”, “lactation” and “breastfeeding”. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.
Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in the final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm was rated as displayed in Table 2.

**Results**

**Indications for use**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction[12]</td>
<td>B1</td>
</tr>
<tr>
<td>Premature ejaculation[13]</td>
<td>B1</td>
</tr>
<tr>
<td>Type II diabetes [14]</td>
<td>B1</td>
</tr>
<tr>
<td>Influenza and the common cold[15]</td>
<td>B1</td>
</tr>
<tr>
<td>Memory improvement[16-18]</td>
<td>B2</td>
</tr>
<tr>
<td>Improved cognitive function[19-22]</td>
<td>B2</td>
</tr>
<tr>
<td>Enhanced physical function[23]</td>
<td>B2</td>
</tr>
<tr>
<td>Chronic bronchitis (with antibiotics)[24]</td>
<td>C</td>
</tr>
<tr>
<td>Cancer prevention[25, 26]</td>
<td>C</td>
</tr>
<tr>
<td>Parkinson’s disease[27]</td>
<td>E</td>
</tr>
</tbody>
</table>

Indications and warnings for use and safety during pregnancy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-estrogenic[28]</td>
<td>1a</td>
</tr>
<tr>
<td>Treatment of intrauterine growth retardation[29]</td>
<td>1b</td>
</tr>
<tr>
<td>Estrogenic[30]</td>
<td>2</td>
</tr>
<tr>
<td>No evidence to support androgenization[31, 32]</td>
<td>2</td>
</tr>
<tr>
<td>Protection of neonatal brain against ethanol damage[33]</td>
<td>3</td>
</tr>
<tr>
<td>Teratogenicity[34-37]</td>
<td>3</td>
</tr>
</tbody>
</table>
A randomized controlled trial of 384 women receiving either ginseng extract or placebo for 16 weeks showed that the beneficial effects in the treatment of menopause are most likely not mediated by hormone replacement-like effects, as physiological parameters such as FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH were not affected by the treatment[28]. On the other hand, there are case reports and animal studies indicating potential estrogenic activity due to ginseng. Evidence includes postmenopausal vaginal bleeding, increased serum ceruloplasmin oxidase activity and phytoestrogenic actions of ginsenoside Rb1[40-46]. A review article on the potential value of plants as sources of anti-fertility agents also reported that Korean ginseng has estrogenic activity[30].

Zhang et al. (1994) conducted a comparison study on pregnant women with intrauterine growth retardation (IUGR)[29]. One group of women received ginseng while the other group was nutritionally treated as controls[29]. The height of fundus, fetal biparietal diameter, urinary estrogens/creatinine, serum human placental lactogen and neonatal weights approached normal pregnancy values[29]. The authors did not report any adverse effects associated with ginseng supplementation[29].

A case was reported of a 30-year-old woman who gave birth to a full-term baby boy with signs of androgenization following ingestion of “ginseng” during her pregnancy[32]. After further investigation, the herbal preparation used by the mother appeared to be adulterated by the herb silk vine (Periploca sepium)[31].
Okamura et al. (1994) reported that ginseng extract prevented an ethanol-induced reduction of neonatal brain weight in rats[33]. The ginseng saponins, including ginsenosides Rg1, Rb2, Rd, Rf and Re, were shown to stimulate a potent recovery of cerebellum growth[33].

Chan et al. have demonstrated that ginsenosides Rb1, Rc, and Re exert direct teratogenic effects on rat embryos[34, 37]. A separate group of investigators also found embryotoxicity when rat and mice whole embryos cultures were exposed to high concentrations of the two ginsenosides Rg1 and Rb1[35, 36] Ginsenosides from Panax ginseng were found to activate DNA polymerase delta in bovine placenta[38].

Researchers conducted a review of the herbs used during pregnancy in Singapore[39]. Panax ginseng was used in various combinations and in various amounts in herbal prescriptions during pregnancy[39]. The researchers could not confirm that the claims made by Chinese herbalists on the efficacy of Panax ginseng in pregnancy were real or not[39]. They concluded that there is no specific effect on pregnant woman, but that it does not exclude the possibility of a beneficial psychosomatic effect[39]. The researchers also noted that the active principles can cross the placenta and reach the fetus[39]. The authors did not discuss if Panax ginseng was safe or contraindicated during pregnancy[39].

<table>
<thead>
<tr>
<th>Use and safety of ginseng during lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk[47-49]</td>
</tr>
<tr>
<td>Level</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Cows with subclinical mastitis caused by Staphylococcus aureus were given subcutaneous injections from an extract of the Panax ginseng root[47]. Based on blood leukocyte measurements, ginseng treatment was found to activate the innate immunity of cows and
contribute to the cow's recovery from mastitis[47]. The authors did not report any adverse effects associated with the use of Panax ginseng during lactation[47]. Two other studies by the same authors conducted in lactating cows found similar results where Panax ginseng increased leukocyte activity and no adverse effects were reported[48, 49].

**Toxicity and adverse effects**

Very low incidence of toxicity has been observed in ginseng clinical trials using well-characterized preparations[50]. When used inappropriately, Panax ginseng has been noted to cause hypertension, diarrhea, sleeplessness, mastalgia, eruptions and vaginal bleeding[1]. Siegel has coined a condition called “ginseng abuse syndrome” in reference to the long-term effects of ginseng use. This ‘syndrome’ is characterized by hypertension, nervousness, sleeplessness, skin rash, diarrhea, confusion, depression, or depersonalization[51].

**Pharmacology**

It is clear that Panax ginseng is pharmacologically active. While it is uncertain to what extent isolated constituents are biologically active, the ginseng saponins (or ginsenosides) are considered to be responsible for a majority of this species’ biological activity[52]. Ginsenosides are unique to Panax ginseng and over 30 of these compounds have been identified[1].

Some of the known pharmacological effects are detailed in Table 3 and attest to the wide range of potential therapeutic applicability of this incredibly popular and seemingly potent herbal medicine.

**Drug Interactions**

There is some evidence of potential interactions between ginseng and prescription drugs, however most of the evidence is derived from preclinical assays. Confirmation from pharmacokinetic studies should be conducted to establish true interactions. Current evidence requires that Panax ginseng be used with caution in conjunction with the following agents:
• Anticoagulant drugs[53, 54]
• Antidiabetic drugs[55]
• Antipsychotic drugs[56]
• Caffeine[57]
• Furosemide[58]
• Immunosuppressants[26]
• Insulin[57]
• Monoamine Oxidase Inhibitors[59, 60]
• Stimulant drugs[61]
• Warfarin (Coumadin)[53, 54, 62]
Discussion

Panax ginseng is frequently used as a general tonic or "adaptogen" to fight stress and possibly to enhance physical and mental performance. This herb is not specifically used during pregnancy and lactation in the same way that ginger might be used to treat nausea and vomiting or how horse chestnut seed extract might be used to treat varicose veins[63, 64]. However, the fact that it is one of the most commonly used herbs worldwide, inevitably women will end up taking the herb during pregnancy or while breastfeeding. As such, it is critical that both women and clinicians be aware of the possible risks attendant to such usage and to be able to plan and advise accordingly.

There is no high-grade evidence demonstrating that P. ginseng is unsafe during pregnancy and lactation. Observations during a cohort and from traditional use have not uncovered any adverse events from ginseng with respect to pregnancy and lactation. A single case report was found in the literature that reported on a potential link between P. ginseng use by a pregnant woman and the death and androgenization of her fetus[31]. It was determined that the ginseng-containing-product was adulterated, however, and as such we cannot infer that ginseng was the causative agent. In addition, this is an isolated case and the anecdotal nature of the evidence does not provide anything beyond speculation. Of somewhat greater concern, however, are the repeated findings of teratogenicity in mice and rats when exposed to ginsenosides. Again this evidence must be interpreted with caution as it is derived from animal embryos and is based on exposure to isolated ginsenosides at much higher levels than achievable through normal consumption in humans. Evidence regarding phytoestrogenic activity of P. ginseng is conflicting; some concern may be justified regarding this possibility especially with respect to exposure during early fetal development.
Our study is limited primarily by the lack of evidence available. Given the vulnerabilities of a developing fetus and newborn child, and the fact that their metabolism can vary substantially from the adult, extreme caution is required in making recommendations for women of child bearing age. The totality of the evidence that we analysed in our systematic review indicates that *Panax ginseng* may well be safe for consumption during pregnancy; however, to ensure safety to the developing fetus, consumption of this herb is best avoided especially during the first trimester.

No human evidence could be found regarding the safety of consuming *Panax ginseng* while breastfeeding. Nonetheless, there is *in vitro* evidence based on three animal studies that *Panax ginseng* was of minimal risk when consumed by lactating cows. Research is necessary to determine if ginsenosides and other potentially active compounds are carried in the human breast milk and also how this might affect a newborn child.

There is evidence to support the use of *Panax ginseng* in the treatment of male sexual dysfunction; care of type II diabetics; amelioration of symptoms from influenza and the common cold; and to enhance cognitive and physical function, however more research is necessary to establish its use in these areas as well as to establish safety during pregnancy and lactation.

**Acknowledgements**
The Canadian College of Naturopathic Medicine
Motherisk – Sick Kids Hospital
University of Toronto
McMaster University
Table 1. Levels of evidence for efficacy

<table>
<thead>
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<th>GRADE</th>
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<tr>
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**Table 2. Levels of evidence for harm**

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<th>LEVEL</th>
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<tr>
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<td></td>
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</tr>
<tr>
<td>3</td>
<td>IN VITRO SCIENTIFIC EVIDENCE</td>
</tr>
<tr>
<td></td>
<td>Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.</td>
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<tr>
<td>4</td>
<td>THEORETICAL EVIDENCE</td>
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<tr>
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<tr>
<td>5</td>
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Table 3: Pharmacological actions attributable to *Panax ginseng*

<table>
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<th>SYSTEM</th>
<th>PHARMACOLOGICAL ACTION</th>
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</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>• Ginsenosides increase serum cortisol levels, stimulate adrenal function and in women, increase dehydroepiandrosterone sulfate (DHEA-S) [65-68]</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Ginsenoside Rb1 may lowers blood pressure and acts as a CNS depressant[11]</td>
</tr>
<tr>
<td></td>
<td>• Ginsenosides interfere with platelet aggregation and coagulation[47]</td>
</tr>
<tr>
<td></td>
<td>• <em>Panax ginseng</em> may lower cholesterol and triglycerides[18]</td>
</tr>
<tr>
<td>Antiinflammatory and antiinfective</td>
<td>• Ginsenosides have analgesic and anti-inflammatory effects[18]</td>
</tr>
<tr>
<td></td>
<td>• <em>Panax ginseng</em> has shown inhibitory activity on Helicobacter pylori[69]</td>
</tr>
<tr>
<td></td>
<td>• <em>Panax ginseng</em> promotes the growth of normal intestinal flora while inhibiting Clostridial species[70]</td>
</tr>
<tr>
<td></td>
<td>• The protein isolate panaxagin may have antiviral and antifungal activity where it appears to inhibit HIV reverse transcriptase and ribosomal activity of some fungi[9]</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>• Ginsenosides potentiate nerve growth factor and may have a neuroprotective effect through nicotinic activity[11, 71]</td>
</tr>
<tr>
<td></td>
<td>• <em>Panax ginseng</em> increases penile vibratory threshold and reduces the amplitude of penile somatosensory evoked potentials[13]</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>• Ginsenosides have anti-asthmatic effects through the relaxation of human bronchial smooth muscle by stimulating the release of nitrous oxide from airway epithelium[72]</td>
</tr>
</tbody>
</table>
| Endocrine system | • *Panax ginseng* may prevent insulin resistance and change gene expression in Type II diabetes[73]  
• Some studies report that *P. ginseng* has phytoestrogenic properties [40-46] |
REFERENCES


69. Belogortseva, N.I., J.Y. Yoon, and K.H. Kim, *Inhibition of Helicobacter pylori hemagglutination by polysaccharide*


MotherNature: Establishing a Canadian Research Network for Natural Health Products (NHPs) During Pregnancy and Lactation

Gideon Koren MD1,2
**Error! Contact not defined.** ND PhD (cand.)1,3
Laura Magee MD4
Sunita Vohra MD5
Doreen Matsui MD6
Anick Béard PhD7
Brad Johnson ND PhD (cand.)5
Myla Moretti MSc1
Adrienne Einarson RN1

11) Motherisk, Hospital for Sick Children, Toronto
12) Division of Clinical Pharmacology and Toxicology, University of Toronto
13) Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto
14) Obstetric Medicine, BC Women’s Hospital
15) Department of Pediatrics, University of Alberta
16) Department of Pediatrics, University of Western Ontario
17) Department of Pharmacy, University of Montreal

Word count: 1,539

Tables: 0

**Correspondence:**
Jean-Jacques Dugoua ND PhD (cand.)
The Hospital for Sick Children
Motherisk Program
Division of Clinical Pharmacology and Toxicology
555 University Avenue
Toronto, ON M5G 1X8
Tel: (416) 813-5781
Fax: (416) 813-7562
jeanjacques.dugoua@utoronto.ca

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ABSTRACT

Background: It has been estimated that between 7 and 55% of expectant mothers use herbal medicines or other types of natural health products (NHPs). Unfortunately, the safety and efficacy of NHPs during pregnancy and lactation is largely unknown. The Motherisk Program is the major Canadian group to counsel and monitor outcomes of women using medications or NHPs, or of women exposed to chemicals, radiation or infection during pregnancy and lactation.

Objective: To create a network for research on NHPs during pregnancy and lactation by forming longstanding collaborations among Canadian medical and complementary and alternative medicine (CAM) practitioners and scientists.

Methodology: Mother-Nature Network members participated in three 2-day workshops and three conference calls throughout the length of this study. Each member was responsible to lead one theme and address the following: initiation, development, presentation and synthesis of comments of all members on the designated theme.

Results: We prioritized areas in high need for future research and collaborative means to conduct such research. NHPs were prioritized as to their importance for future study. Areas for the prospective collection of data on NHP use in pregnancy and lactation were identified. A research and business plan was developed for the long-term sustainability of the Network.

Conclusion: The Mother-Nature Network is well situated to create a new climate in Canada, where data are collected and interpreted on the effects and safety of NHPs during pregnancy and lactation.
Introduction

The Motherisk Program is a Toronto-based group counselling and following-up outcomes of women using medications or exposed to chemicals, radiation or infection during pregnancy and lactation.

During the last few years, it has become apparent that despite thousands of Canadian women using natural health products (NHPs) during pregnancy and lactation, there are poor evidence-based human data on the safety of these products. There is an urgent need for research networking throughout Canada among health professionals, conventional as well as complementary and alternative medicine (CAM) providers, to move toward evidence-based use of NHPs during pregnancy and lactation.

The Motherisk Program has initiated the creation of the MotherNature Network to help close the knowledge gap on the safety of NHPs in pregnancy and lactation.

Background

According to a 2002 survey by the Natural Health Products Directorate (NHPD), the division of Health Canada responsible for registering and monitoring natural health products (NHPs) in Canada, 71% of Canadians have used some form of NHP1. Twenty nine percent (29%) feel that NHPs are natural and safe or better than conventional medications1.
Although the NHPD does not provide data on the use of NHPs during pregnancy and lactation\(^1\), it is believed that NHP use by pregnant and breastfeeding women is quite common where one study reported herbal medicine use during pregnancy at 7% to 55%\(^2\). According to the Motherisk Program of the Sick Kids Hospital, over 6,000 callers every year seek advice about the safe use of NHPs, such as vitamin A, Echinacea and St. John’s wort, during their pregnancy\(^3\). According to a survey of midwives in the United States, between 45% to 93% of midwives will prescribe some form of NHP to women during their pregnancy\(^4\). Of the midwives who used herbal preparations, 64% used blue cohosh, 45% used black cohosh, 63% used red raspberry, 93% used castor oil and 60% used evening primrose oil\(^4\).

NHP use by pregnant women could be due to a paradoxical response to the decreased use of prescribed medications during pregnancy for fear of teratogenicity. In a study on the pharmaceutical drug use of 295 pregnant women, 37% of these women reported non-compliance with their existing drug regimen due to hesitations on drug use during pregnancy\(^5\). For many women, therefore, NHPs may seem a reasonable alternative to pharmaceutical drugs as the lay media often portrays natural medicines as “safe”. In addition to intended NHP use during pregnancy, there is a concern of accidental NHP exposure by the mother and fetus as many pregnancies are unplanned. For example, the herbal medicines chastetree and evening primrose oil are frequently used by women in the treatment of premenstrual syndrome and cystic mastalgia\(^6-9\).
Despite the prevalent use of NHPs by pregnant women, there is very little published evidence with regards to the safety and efficacy of NHPs during pregnancy and lactation. Many modern and classic texts warn against the use of herbal medicines during pregnancy or lactation for up to one-third of the products listed in their monographs\textsuperscript{10}. However, most resources provide little information on the data used to evaluate reproductive toxicity apart from reports of historical use of herbs as abortifacients or uterine stimulants or animal data of genotoxicity or teratogenicity\textsuperscript{10}.

The objective of this initiative was to create a network for research on NHPs during pregnancy and lactation by forming longstanding collaborations among Canadian medical and CAM practitioners and scientists. Specific objectives included:

- identification of knowledge gaps (highest priority),
- choice of best methodologies to address these knowledge gaps, and
- initiating research protocols to close the knowledge gaps.

**Methodology**

Between 2004-2005, MotherNature Network members participated in three 2-day workshops and three conference calls. Each member was assigned a theme and was asked to address the following: initiation, development, presentation and synthesis of comments of all members on the designated theme.
Results and Discussion

Phase 1: Identifying the knowledge gap

The first phase of MotherNature activities was the identification of available data in order to better define knowledge gaps and areas that need original research. Based on systematic reviews from the textbook entitled “Herbal Medicine in pregnancy and lactation – An evidence-based approach” by Mills, Dugoua, Perri & Koren (2006), from Dr. Boon’s evidence-based group and from the Motherisk database of reviews of CAM safety in pregnancy, the following knowledge gaps were identified:

1. The emmenagogue-uterotonic potential of NHPs

   Traditional texts identify scores of NHPs, which are believed and/or have been used by different traditions to induce labor. In the vast majority of cases this labeling is based on total lack of experimental evidence-based science, and in a few cases, based on low quality science. Although there do exist some well-conducted clinical studies on NHPs during pregnancy, such as red raspberry and castor oil, these are rare.

2. The fetal safety of NHPs

   Presently, few epidemiological human studies are available on the vast majority of NHPs with respect to teratogenic potential. Over the last decade, Motherisk has completed studies on echinacea, ginger and glucosamine sulfate, but for hundreds of products – no such studies are available.
Phase 2: Identifying research methodologies to address the gaps

The second phase of MotherNature focused on in-depth discussion of methodologies and methodological challenges as related to addressing the gaps identified in Phase 1. The following are the key methodological considerations identified by the MotherNature Network:

1. NHPs are used by large numbers of Canadian women.
2. Several provinces (e.g., Quebec, Manitoba, Saskatchewan) have drug programs, where all prescribed medications are paid by the program and, hence, can be identified and linked to pregnancy outcomes, if the woman took them in pregnancy. However, these programs do not pay for NHPs as physicians do not frequently prescribe them. Hence, unlike medicinal drugs, the ability to conduct population-based research by linking such national databases does not exist for NHPs.
3. Any research linking NHPs use in pregnancy with outcomes of interest (e.g., uterotonicity or birth defect) must stem from interviews with women either in pregnancy, or postpartum or both.

Phase III: Addressing the uterotonic potential of NHPs

Several different research approaches have been identified in order to address which NHPs cause uterine contraction and which do not:

Midwife Survey

The MotherNature Network believes it will be essential to research midwives as to the emmenogogue and uterotonic NHPs they use, and
critically, the type of evidence their observations can bring forward. Since Canadian midwives are regulated health professionals in the majority of provinces and territories (British Columbia, Alberta, Manitoba, Ontario, Quebec, Northwest Territories, Saskatchewan (pending) and Nova Scotia (pending)), they are obligated to maintain detailed patient files. It is assumed that midwives would record in the charts if their patients had consumed NHPs or been prescribed NHPs during their pregnancy, and would also chart the birth outcome. With this charted information, the safety of uterotonic NHPs could be determined both prospectively or retrospectively. Should either the midwife prospective or retrospective cohort demonstrates safety for a particular uterotonic NHP, a randomized controlled trial (RCT) could possibly be approved by a research ethics board (REB) to determine the NHPs’ efficacy.

**Canadian Perinatal Network National study**

The Canadian Perinatal Network is conducting a National study on the etiologies of preterm labor. We have already identified the questions to be asked and a list of NHPs claimed to be emmenogogues and uterotonics to be included in this study. The data obtained from this national study could provide the Network data regarding the most commonly used NHPs by pregnant Canadians. The data may indicate associations between NHP intake by the mother and preterm labour. However, the risks of preterm labour are multiple, including bacterial vaginosis, smoking, alcohol and substance abuse among others. Drawing a direct causal relationship between NHP use and preterm delivery is not possible
from such a reporting system, but results from the national study may highlight future studies to determine causal relationships, if any.

Mount Sinai Hospital case-control study

The Motherisk Program will commence a case-control study at Mount Sinai Hospital to investigate use of NHPs among women hospitalized for premature contractions, as compared to a control group that is hospitalized to give birth at term. As discussed above in the Canadian Perinatal Network National Study, the Mount Sinai study poses the same challenges in interpreting results.

Phase IV: Assessing Fetal Safety of NHP:

Two research methodologies have been identified.

Nested Case Control Study

In Quebec, there is a province-wide database of congenital malformations. A feasibility study will be developed to ask mothers of children with specific malformations through questionnaire on their use of selected NHPs during embryogenesis (first trimester of pregnancy). The data obtained from the Quebec database may highlight frequently used NHPs in the first trimester of pregnancy. As per the challenges discussed above for the national and case-control studies, adverse event associations (if any) will have to be interpreted with caution.
Motherisk Program prospective studies

The Motherisk Program will continue to develop and implement national prospective, controlled observational studies of pregnancy outcomes after specific NHPs use in early pregnancy. The challenge for MotherNature will be to increase enrollment to these studies through partners and stakeholders in Canada, the US, and worldwide. Since Motherisk counsels over 6,000 callers yearly on issues related to NHP use during pregnancy, it is ideally situated to design prospective cohort studies to determine safety and if safe, to design RCTs to determine efficacy.

Conclusion

The MotherNature Network was built on the expertise of Motherisk, IMAGE and FRAME programs over the last two decades, on the members and on the stakeholders of this study. The MotherNature Network has created tools for standardized and coordinated collection, interpretation and dissemination of NHP safety data in pregnancy and lactation. The MotherNature Network is well situated to create a new climate in Canada, where data are collected and interpreted on the effects and safety of NHPs during pregnancy and lactation.

References

1. NHPD. Natural Health Product Directorate - Baseline Natural Health Products Survey Among Consumers. March 2005.


Appendix C

Published manuscripts not appropriate to the theme of the thesis


Astragalus-Based Chinese Herbal Combinations for Advanced Non–Small-Cell Lung Cancer: A Meta-Analysis of 65 Clinical Trials Enrolling 4,751 Patients

Jean Jacques Dugoua ND, PhD (1)
Ping Wu MB ChB, MSc (2)
Dugald Seely ND, MSc (3)
Ogenowede Eyawo MPH (4)
Edward Mills PhD (4,5)

1) Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada
2) Shanghai Hospital #4, Shanghai, China
3) Department of Clinical Epidemiology, Canadian College of Naturopathic Medicine
4) Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada
5) Faculty of Health Sciences, University of Ottawa, Ottawa, Canada
Abstract

Background: Non-small-cell lung cancer (NSCLC) is a leading cause of death. Interventions to reduce mortality in patients with NSCLC represent a patient-important field of research. Little is known about interventions used outside of the Western world for NSCLC. One intervention widely used in Asia is astragalus-based herbal preparations.

Methods: We conducted a comprehensive systematic review of all published randomized clinical trials (RCTs) evaluating astragalus-based herbal preparations in NSCLC patients. We searched independently, in duplicate, 6 English language electronic databases and 2 Chinese-language databases. We abstracted data independently, in duplicate on studies reporting of methods, survival outcomes, tumor responses, and performance score responses. We applied a random-effects meta-analysis and report outcomes as Relative Risks (RR) with 95% Confidence Intervals (CIs).

Results: We included 65 RCTs enrolling 4,751 patients. All trials included the herbal preparations plus platinum-based chemotherapy versus the chemotherapy alone. We pooled 7 studies (n=529) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45-0.65, P=<0.0001). We included 20 trials in (n=1520) for survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54-0.79, P=<0.0001). This effect was consistent at 24 and 36 months. When we applied a composite endpoint of any tumor treatment response we pooled data from 57 trials and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26-1.44, P=<0.0001). Statistical heterogeneity was low across trials.

Limitations: The quality of reporting the RCTs was generally poor. There is also reason to believe that studies reported as randomized may not be.

Conclusions: We found a large treatment effect of adding astragalus-based herbal treatment to standard chemotherapy regimens. There is a pressing need for validation of these findings in well-conducted RCTs in a Western setting.
INTRODUCTION

In the United States, lung cancer is the leading cause of death in both men and women where the incidence is 31% and 27%, respectively\(^1\). In women, lung cancer is the leading cause of death, although the death rates stabilized between 1995-2001 after two decades of increases\(^1,2\). In men, death rates related to lung cancer have substantially declined from 1995-2001\(^2\).

The most common form of lung cancer is non–small-cell lung cancer (NSCLC), which accounts for 75% of all lung cancer occurrences. In the last few decades, new systemic treatments for advanced NSCLC have demonstrated low efficacy and high toxicity. When compared to surgery alone, meta-analyses have shown that adjuvant treatment with chemotherapy reduces the risk of death at 2 years by 13\(^3\), adjuvant treatment with chemoradiotherapy reduces that risk by 14\(^4\) and adjuvant radiotherapy alone increases that risk by 21\(^5,6\). Adding platinum-based chemotherapy drugs to standard chemotherapy protocols increased 12-month survival by only 5% and tumor response by 62%, however these drugs have significant hematologic toxicity and nephrotoxicity and adverse effects, such as nausea and vomiting\(^7\). A meta-analysis demonstrated that the 12-month survival rate following platinum-based regimens was 34% (95% CI, 33\%-36\%)\(^7\). A recent phase III randomized controlled trial (RCT) demonstrated that the addition of the drug gefitinib, an epidermal growth factor receptor tyrosine kinase-inhibitor, to carboplatin/paclitaxel chemotherapy had no additional benefit on survival or time to progression\(^2\). Based on these poor treatment outcomes and treatment toxicity to patients with NSCLC, there is a need for alternate treatment approaches.

In China, herbal medicines, commonly referred to as traditional Chinese medicines (TCM), are frequently combined with chemotherapy for the treatment of lung cancer. The herb astragalus (Astragalus membranaceus) may potentiate host immune function by stimulating macrophage and natural killer cell activity\(^3\) and enhance immune recognition of lung cancer cells by inhibiting production of T-helper cell type 2 cytokines\(^4\). When compared to treatment with platinum-based chemotherapy alone, a RCT demonstrated that treatment with astragalus in combination with platinum-based chemotherapy
significantly reduced risk of death at 12 months (risk ratio [RR] = 0.62; 95% CI, 0.43-0.89) and 24 months (RR = 0.75; 95% CI, 0.58-0.97).6

There are a large number of published RCTs on astragalus-based Chinese herbal medicines combined with platinum-based chemotherapy.6 Our objective is to systematically review the scientific literature for RCTs on astragalus treatment combined with platinum-based chemotherapy and to meta-analyze the pooled data from these RCTs. Should the results be favorable, astragalus-chemotherapy combination treatment may provide an important step forward for new interventions for patients with NSCLC.

METHODS

Study Inclusion Criteria
We included any study that randomized patients with advanced NSCLC, provided the treatment group with Chinese herbal medicines containing the herb astragalus in combination with standard platinum-based chemotherapy, provided the control group with platinum-based chemotherapy alone, and reported data on at least one of our outcomes of interest (survival, tumor response, or performance status) with sufficient detail to permit calculation of the risk ratios of each outcome. We excluded pharmacokinetic studies and non-randomized trials. We excluded studies that reported only laboratory values rather than clinical responses. We also excluded direct comparisons of TCM formulations.

Search strategy
Three reviewers (PW, EM and YH) assessed eligibility based on the full text papers and conducted data extraction, independently, using a standard pre-piloted form. Disagreements were resolved by consensus or by a third reviewer. If the required information was not available in the published article, we obtained additional information in correspondence with the authors. We included all evaluated outcome measures including: survival at 6, 12, 24, and 36 months, disease stage, Karnofsky performance (KP), and the response evaluation criteria in solid tumors (RECIST). The response is categorized as complete response (CR), partial response (PR) outcomes, stable disease (SD), progressive disease (PD) and as CR + PR as a composite for response rate (RR).

In addition, we extracted data on trial quality, protocol, and outcomes assessed. We assessed quality through the reporting of the following criteria: sequence generation and allocation concealment. We also noted the language in which the paper was written and the setting the studies were conducted. These criteria were not used for weighting covariates in the meta-analysis; instead, these were considered a priori explanations for study heterogeneity.

All inclusion and exclusion criteria and the categorization of outcomes were made before any meta-analysis of the data. Our decision to group together for this meta-analysis those studies using platinum-based chemotherapy was based on the fact that this therapy is currently a standard treatment for advanced NSCLC. Following the example set by D’Addario et al7 and the Cochrane Collaboration’s Non–Small-Cell Lung Cancer Collaborative Group,8 platinum-based chemotherapy was grouped together as a therapeutic class when assessing efficacy of treatment for NSCLC. Each stage of the planning, design, analysis, and reporting of this meta-analysis was conducted in accordance with the QUOROM Statement guidelines.9

**Analysis of Outcomes**

**Survival.** Given that all of the studies identified in our systematic search reported crude survival data as the number of patients in each treatment group who died by 6, 12, 24, or 36 months, we calculated the probability of failure (death) as the number of patients who had died by each time point divided by the total
number of patients enrolled at the start of the trial for each treatment group. This approach is intentionally conservative: if some patients dropped out of the study, retaining them in the denominator as we have done would lower the estimate of effectiveness. This is analogous to an intention-to-treat analysis.\textsuperscript{10} The risk ratios of treatment failure (death) at each time point was calculated as the proportion who died in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, compared to the proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors the combination regimen.

\textit{Objective tumor response}. Given that most of the studies identified in our systematic search reported tumor response at conclusion of treatment using RECIST.\textsuperscript{11} we calculated the probability of tumor response as the number of patients experiencing any response (complete response plus partial response) divided by the total number of patients in each treatment group (complete response plus partial response plus no change plus progressive disease). The RR of tumor response was calculated as the probability of tumor response in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen. This is the approach for meta-analysis of tumor response recommended by Sutton et al.\textsuperscript{12}

\textit{Performance status}. Many of the studies identified in our systematic search reported performance status using the Karnofsky performance scale,\textsuperscript{13} with most using a 10-point change as the cutoff for improved or worse performance status, and a few others using a 20-point change as the cutoff. We therefore calculated the probability of improved or stable performance status as the proportion of improved or stable performance status: (> 10-point increase plus no change) divided by the total (> 10-point increase, plus no change, plus > 10-point decrease). The RR of improved or stable performance status was calculated as the proportion of improved or stable performance status in the astragalus-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen.

\textit{Analysis}

We used the random-effects model of DerSimonian and Laird\textsuperscript{14} to estimate the summary RR for each of the four outcomes: risk of death (at 6, 12, 24, and 36 months), tumor response, performance status, and severe
chemotherapy toxicity. We used the I² statistic to assess between-study heterogeneity and interpreted the outcome as <50% as non-problematic heterogeneity. To assess publication bias, we used the Begg-Mazumdar test, which examines the association between the effect estimates of individual studies and their variances; significant correlation between these two factors identifies publication bias.¹⁵
We applied the Relative Risk and 95% Confidence Intervals as our primary effect measure in this analysis. For analysis examining response, favourable results for the TCM intervention are in the direction greater than 1. In circumstances of zero outcome events in either arm of a trial, we used the Haldane method and added 1 to each arm, as suggested by Sheehe¹⁶. We first pooled studies on all interventions versus all controls using the DerSimonian-Laird random effects method¹⁷. This method recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. We calculated the I² statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity¹⁸. Forest plots are displayed for the primary analysis, showing individual study effect measures with 95% CIs and the overall DerSimonian-Laird pooled estimate. We conducted a meta-regression analysis using the unrestricted maximum likelihood method to determine if the a priori covariates of TCM formulation yielded differing effects. We examined publication bias visually and through the Begg-Mazumdar tests. We calculated the optimal information size (OIS) required to determine adequate power across trials. We used Stats Direct and Comprehensive Meta-Analysis (Version 2) for all statistical procedures. All p-values are 2-sided and a p-value <0.05 was considered significant. PW and EM conducted the analysis.

RESULTS

Included studies
Our systematic search identified 1,385 potentially relevant abstracts, of which 221 were identified as requiring full-text article retrieval. Close screening of these 221 studies identified 65 studies that met our inclusion criteria, containing a total of 4,751 patients. Most studies were small (median 67, Interquartile range 56-83). Studies poorly reported methodological issues including sequence generation (25%), allocation concealment (3%), and reporting of adverse events (67%). Table 1 provides the study characteristics.
Survival

We pooled 7 studies \(^{19-25}\) (n= 529) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45-0.65, \(P=0.0001\), \(I^2=0\%\), 95% CI, 0-58\%, \(P=0.74\), See Figure 2). We included 20 trials \(^{5, 20-38}\) in (n=1520) in our analysis of survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54-0.79, \(P=0.0001\), \(I^2=74\%\), 95% CI, 57-82\%, \(P<0.0001\), See Figure 3). As 12-month survival was our primary outcome, we applied the publication bias assessment and found no evidence of publication bias (Kendall’s \(\tau = -0.157\), \(P=0.31\)). We included 13 trials \(^{5, 22, 24, 25, 30-38}\) (n=1,090) with survival rates reported at 24 months and found a pooled RR of 0.74 (95% CI, 0.66-0.84, \(P=0.0001\), \(I^2=64\%\), 23-78\%, \(P=0.0008\), See Figure 4). We included data from 10 trials \(^{5, 25, 30-36, 38}\) (n=878) reporting on survival at 36 months and found a pooled RR of 0.86 (95% CI, 0.80-0.92, \(P<0.0001\), \(I^2=29\%\), 95% CI, 0-65\%, \(P=0.17\), See Figure 5).

Tumor Response

We were able to include data from 27 trials \(^{27, 29-33, 39-59}\) (n=1,759) reporting on complete responses to treatment and found a pooled RR of 1.43 in the direction of favorable outcomes for herbal-based treatment (95% CI, 0.98-2.10, \(P=0.07\), \(I^2=0\%\), 95% CI, 0-42\%, \(P=0.99\)). The same 27 trials reported on partial response to treatment and found a pooled RR of 1.35 favoring herbal treatment (95% CI, 1.19-1.53, \(P=0.0001\), \(I^2=0\%\), 95% CI, 0-38\%, \(P=0.99\)). When we applied a composite endpoint of any treatment response we pooled data from 57 trials \(^{20, 22, 23, 27, 29-35, 38-76, 5, 24, 25, 77-79}\) and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26-1.44, \(P=0.0001\), \(I^2=0\%\), 0-28\%, \(P=0.99\), See Figure 5).

Performance Status

We included data from 35 trials \(^{5, 25, 27, 33, 38-42, 44, 45, 47-53, 55-61, 66, 69, 73, 74, 76, 77, 80-83}\) (n=2,650) assessing stable or improved Karnofsky scores and found a pooled RR of 1.58 (95%, 1.39-1.81, \(P=0.0001\), \(I^2=69\%\), 55-78\%, \(P<0.0001\)).

DISCUSSION

Our findings should be of interest to cancer researchers and funding agencies. We found consistent evidence of improved survival and tumor response in astragalus-based herbal medicine therapy combined with platinum-based chemotherapy compared with platinum-based chemotherapy alone, the standard of care. While there is reason to be cautious of the quality of the included clinical trials, due to their small
sample sizes and inadequate reporting of methodological issues, there has been a consistent direction of
treatment effect that warrants further examination by experienced clinical trialists in a transparent manner.

Our study has both strengths and limitations to consider. Strengths include our extensive searching and
identification of Chinese clinical trials that few systematic review groups may be able to accomplish. Our
analysis used a broad approach that considered all astragalus containing herbal combinations as
comparatively similar, thus allowing much greater power to detect an effect over a single trial. It is possible
that specific combination exert a differing therapeutic effect, however we were unable to identify such
specific formulations. Limitations of our study are predominantly related to the need for caution in
interpreting the clinical trials. There is consistent evidence that publication bias may exist in Chinese
medical journals and thus, only positive trials are published. A recent evaluation, by Wu et al., found that
many studies labelled as RCTs with Chinese journals were, in fact, not randomized. In our own
experience, we recognize many Chinese clinical trialists have not been exposed to appropriate clinical
epidemiology training. Yet even if our analysis includes predominantly non-randomized studies, the
consistency of therapeutic effect warrants further examination. Other systematic reviews of published
studies from Chinese journals have identified specific journals with better study quality, and also found
trends in improvement of study quality over time. We assessed publication bias in our primary outcome
(survival at 12 months) and did not find statistical evidence of bias, although funnel plots and statistical
tests cannot identify the absence of publication bias. The reporting of quality features including how trials
were randomized and how allocation concealment was achieved adds further caution to our study
interpretation. While the inadequate reporting of these items is desirable, there is, as yet, conflicting
evidence that the reporting of these issues affects the magnitude of treatment effect.

Given the consistency of treatment effect, large number of trials, importance of the disease and the caution
about study quality it seems only reasonable that a clinical trial should be conducted in a Western setting
that can ensure adequate sample size and concealed allocation to study arms. Such a clinical trial would
provide strong inferences into the believability of our meta-analysis findings and could massively impact
drug development. However, until a trial is conducted, we recommend counseling interested patients to
maintain cautious optimism on any treatment effect and discuss with their oncology physician about potential costs and harms.

Our study builds on an existing collaboration between researchers in China and in North America. We recognize that important and effective drugs have been discovered by examining the Chinese medical literature for existing clinical trials. Artemisin-based therapy for malaria and Oseltamivir (tamiflu) for influenza are two compelling examples.\textsuperscript{90, 91} We have previously used this approach for examining potentially effective interventions for hepatocellular cancers (unpublished) and found evidence of existing interventions that have never been evaluated in the West, despite compelling evidence of effectiveness. We believe that this approach represents a low-cost approach to identifying potentially effective new opportunities for drug development.

Additional research is needed to further understand the specific immunologic and cytotoxic mechanisms that \textit{astragalus} may impact as an adjunct to chemotherapy for the treatment of advanced NSCLC.

\textbf{Authors’ Disclosures of Potential Conflicts of Interest}

The authors indicate no potential conflicts of interest.

\textbf{Acknowledgement:} This study was generously supported by the Lotte and John Hecht Memorial Foundation.
Figure 1. Flow diagram of included studies.

- Potentially relevant RCTs (n=1484)
- Abstracts excluded as irrelevant (n=1320)
- Full text paper obtained for further review (n=164)
- 99 studies further excluded:
  - No Astragalus involved in TCM treatment. (n=54)
  - Not all subjects received Astragalus based TCM. (n=8)
  - No Platinum included in the chemotherapy or chemotherapy combined with radiotherapy. (n=10)
  - No usable endpoints were included. (n=16)
  - Not a controlled trial (n=3)
  - Duplicated study (n=4)
  - Not all subjects suffered from NSCLC. (n=4)

Studies included in final meta-analysis. (n=65)
Relative risk meta-analysis plot (random effects)

Figure 2. Six-month survival with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Figure 3. Twelve-month survival with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Figure 4. Twenty-four-month survival with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Figure 5. Thirty-six-month survival with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
Figure 6. Tumor response with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

Wang WR 2.00 (1.17, 3.62)
Yang QR 1.98 (1.21, 3.52)
Lin HS 5.22 (3.41, 8.30)
Zhong Y 1.09 (0.27, 4.35)
Zhou Q 1.38 (1.12, 1.86)
Tian JH 1.14 (0.52, 2.56)
Mao CH 2.00 (1.11, 3.80)
Zhang HT 3.60 (1.60, 8.63)
Li DF 2.20 (1.00, 5.08)
Chen GY 2.17 (0.83, 6.01)
Liu LS 1.14 (0.52, 2.56)
Xue YB 2.00 (1.13, 3.72)
Xu YQ 5.71 (1.02, 34.48)
Li L 1.18 (0.65, 2.19)
Luo SZ 2.25 (0.85, 6.27)
Feng L 1.25 (0.58, 2.72)
Yang C 2.17 (1.09, 4.71)
Kong YZ 13.36 (1.87, infinity)
Wen HY 2.85 (1.08, 7.89)
Xie Y 1.29 (0.35, 4.83)
Luo XL 1.72 (0.70, 4.41)
Liu F 1.71 (0.81, 3.76)
Wang C 1.09 (0.69, 1.68)
Gao P 1.52 (1.12, 2.22)
Zhang XH 1.22 (0.98, 1.60)
Wang DJ 1.30 (1.05, 1.67)
Chu GT 1.35 (1.10, 1.71)
Zhou H 1.65 (1.19, 2.47)
Fan FY 1.15 (0.96, 1.40)
Liu SS 1.52 (1.12, 2.18)
Jia YJ 1.30 (1.00, 1.78)
Zou YH 1.22 (0.98, 1.60)
Liu JX 1.22 (1.06, 1.47)
Liu JX 2.35 (1.85, 3.09)
combined [random] 1.59 (1.39, 1.83)

Figure 7. Stable/improved Karnofsky performance status with Astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.
References


57. Xie Y, He WG. TCM Jianji II combined with NP chemotherapy in advanced non-small cell lung cancer treatment Cancer research and clinic. 2006;18:701-703.


Table 1. Included study characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Protocol*</th>
<th>Ingredients</th>
<th>Stage †</th>
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<td>Cao²⁵</td>
<td>76</td>
<td>CAP/NP + Astragalus combination</td>
<td>Adenophora verticillata, Ophiopogonis japonicus, Schisandra chinensis, Astragalus membranaceus, Oldenlandia diffusa, Eriobotrya japonica, Fritillaria cirrhosa, Arisaema amurense</td>
<td>III/IV</td>
</tr>
<tr>
<td>Chen²²</td>
<td>43</td>
<td>CAP + Astragalus combination</td>
<td>Codonopsis pilosula, Astragalus membranaceus, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Dioscoreae opposita, Oldenlandia diffusa, Houttuynia cordata, Patrina villosa, Scutellaria barbata, Agrimonia pilosa, Ziziphus jujube</td>
<td>III/IV</td>
</tr>
<tr>
<td>Chen⁴⁷</td>
<td>56</td>
<td>NP + Yi Qi Yan Yin</td>
<td>Adenophora, Liriop, rehmanniae praeparatum, Astragalus, radix pseudostellariae, Poria, ligustrum, hawkthorn, Chinese sage, Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Cheng⁶⁴</td>
<td>60</td>
<td>FDH + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Chu⁶⁹†</td>
<td>128</td>
<td>EAP + Radiation + Astragalus combination</td>
<td>Astragalus, Panax ginseng, Atractylodis macrocephala, Psoralea corylifolia, Asparagus cochin chinensis, Ophiopogonis japonicus, Scrophularia ningpoensis, Rehmannia glutinosa, Sparganium stoloniferum, Curcuma zeodoria, Manis pentadactyla, Ostrea gigis shell, Trichosanthes kirilowii, Arisaema amurense, Scutellaria barbata, Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Fan⁷⁴</td>
<td>112</td>
<td>CAP +</td>
<td>Codonopsis pilosulae, Atractylodis</td>
<td>III/IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage †</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Fei CB 2003</td>
<td>68</td>
<td>MVP + Astragalus combination</td>
<td>Astragalus, Codonopsis pilosulae, Rehmannia glutinosae, Asparagus cochinchenensis, Ophiopogonis japonics, Serophulariae ningpoensis, Cimicifuga foetida, Houttuynia cordata, Smilax glabra, Aloe vera</td>
<td>III/IV</td>
</tr>
<tr>
<td>Feng</td>
<td>60</td>
<td>GP + Feiluping II</td>
<td>Astragalus, American giseng, Peach Seed, safflower, petiolate paris [root], Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Gao</td>
<td>96</td>
<td>MVP/CAP + Astragal.</td>
<td>Astragalus</td>
<td>III/IV</td>
</tr>
<tr>
<td>Gao</td>
<td>67</td>
<td>GCN + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Hong</td>
<td>47</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcussenticosus, Mylabirs cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Jia YJ 2004</td>
<td>68</td>
<td>MVP/NP + Astragalus combination</td>
<td>Curcuma longa, Curcuma aromatica, Snake, Prunellae vulgaris, Concha ostrea, Oldenlandia diffusa, Astragalus, Panax quinquefolium</td>
<td>III/IV</td>
</tr>
<tr>
<td>Jin</td>
<td>90</td>
<td>MVP + Astragalus combination</td>
<td>Astragalus, Polygonatum chinense, Ligustricum lucidum, Ganoderma lucidum, Salvia chinensis, Paris polyphylla, Drynaria fortunei, Citrus reticulate</td>
<td>III/IV</td>
</tr>
<tr>
<td>Kong</td>
<td>52</td>
<td>GP + Zhenqifuzhen capsule</td>
<td>Astragalus, ligustrum</td>
<td>III/IV</td>
</tr>
<tr>
<td>Li</td>
<td>114</td>
<td>CE/CAP + Astragalus combination</td>
<td>Astragalus, Polygonatum chinense, Panax ginseng, Agrimonia pilosa, Houttuynia cordata, Rheum palmatum, Polyporus umbellatus, Lobelia chinensis, Oldenlandia diffusa, Arisaema amurense, Coix lachryma, Prunus persica, Trichosanthes kirilowii, Prunella vulgaris</td>
<td>III/IV</td>
</tr>
<tr>
<td>Li</td>
<td>90</td>
<td>CE/CAP + Astragalus combination</td>
<td>Astragalus, Adenophora verticillata, Lilium brownii, Ophiopogonis japonics, Coix lachryma, Scutellaria barbata, Akebia trifoliata, Selaginella doederleinii, Agrimoniae pilosa, Polistes japonicus, Fritillaria thunbergii, Houttuynia cordata, Pinellia ternate, Glycyrrhizae</td>
<td>III/IV</td>
</tr>
<tr>
<td>Li</td>
<td>35</td>
<td>NP + Jian Pi Wen Shen</td>
<td>Astragalus, Atractylodes, Poria, epimedium, cistanche, greater selaginella, Chinese sage</td>
<td>II-IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage †</td>
</tr>
<tr>
<td>------------</td>
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<td>------------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Li ^45</td>
<td>70</td>
<td>NP + Jian Pi Yi Shen</td>
<td>Pantax ginseng, Astragalus, Poria, Atractylodes, dry orangepeel, amomum fruit, Red Paeony Root, ligustrum, cuscuta, eclipta, babchi seed, encommiae ulmoide, epimedium, Wolfberry, polygonatum, hawkthorn, gizzard lining, Liquoric Root</td>
<td>III, IV</td>
</tr>
<tr>
<td>Li L ^50</td>
<td>83</td>
<td>NP + TCM</td>
<td>Astragalus, Atractylodes, Adenophora, dendrobium, ligustrum, Wolfberry, Lily, Chinese angelica, rehmanniae vaporata, hemlock parsley</td>
<td>III/IV</td>
</tr>
<tr>
<td>Li M ^54</td>
<td>40</td>
<td>NP/VP + Yi Qi Hua Tan</td>
<td>Campanumae pilosula, Astragalus, trichosanthes rind, friillary</td>
<td>III/IV</td>
</tr>
<tr>
<td>Lin ^41</td>
<td>202</td>
<td>NP/MVP + Shan-dan capsule</td>
<td>Ginseng, Astragalus, Atractylodes, gizzard lining, trichosanthes, Pinellia, magnolia, hovenia dulcis, curcuma, salvia</td>
<td>I - IV</td>
</tr>
<tr>
<td>Liu ^24</td>
<td>77</td>
<td>MAP + Jin Fu Kang</td>
<td>Astragalus, Adenophora verticillata, Ophiopogonis japonicus, Ligustricum lucidum, Selaginella doederleini, Paris polynylla</td>
<td></td>
</tr>
<tr>
<td>Liu ^77*</td>
<td>190</td>
<td>CAP/MVP + Jin Fu Kang</td>
<td>Astragalus, Adenophora verticillata, Ophiopogonis japonicus, Ligustricum lucidum, Selaginella doederleini, Paris polynylla</td>
<td>II, III or IV</td>
</tr>
<tr>
<td>Liu ^25</td>
<td>144</td>
<td>MAP + Jin Fu Kang</td>
<td>Astragalus, Adenophora verticillata, Ophiopogonis japonicus, Ligustricum lucidum, Selaginella doederleini, Paris polynylla</td>
<td></td>
</tr>
<tr>
<td>Liu ^68</td>
<td>65</td>
<td>EAP/CAP + Astragalus combination</td>
<td>Astragalus, Pseudostellaria heterophylla, Adenophora verticillata, Atractylidis macrocephala, Rehmannia glutinosae, Coix lachryma, Poria cocos, Curcuma zeodoaria, Saliva miltiorrhiza, Panax notoginseng, Citrus aurantium, Cremarora variabilis, Prunus armeniaca</td>
<td>III/IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage†</td>
</tr>
<tr>
<td>-----------</td>
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<td>-----------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Liu F58</td>
<td>60</td>
<td>NP + Fuzhenguben</td>
<td>American ginseng, Astragalus, salvia, Chinese angelica, Heartleaf Houttuynia Herb, dry orangepeel, Thunberg Fritillary Bulb</td>
<td>III/IV</td>
</tr>
<tr>
<td>Lu63</td>
<td>73</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cicho</td>
<td>III/IV</td>
</tr>
<tr>
<td>Lu XC32</td>
<td>96</td>
<td>PAC + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus, senticosus, Mylabirs cicho</td>
<td>III/IV</td>
</tr>
<tr>
<td>Lu YX59</td>
<td>58</td>
<td>NP + Zhongyao Zengmian</td>
<td>Black ant, ancanthopanax, raw oyster shell, Astragalus, polygonatum [root], Epimedium Herb,mulberry, Barbary Wolfberry Fruit, campanumaea pilosula, atractylodes, poria, salvia</td>
<td>III/IV</td>
</tr>
<tr>
<td>Luo SZ51</td>
<td>50</td>
<td>TAX+DDP + Shenqifuzhen injection</td>
<td>Campanumaea pilosula, Astragalus</td>
<td>III/IV</td>
</tr>
<tr>
<td>Luo XL33</td>
<td>108</td>
<td>EP +TCM</td>
<td>Astragalus, Atractylodes, Dried Longan Pulp, rehmanniae praeparatum, white Paeony Root, radix rehmanniae, dry orangepeel, Costustoot, hemlock parsley</td>
<td>III/IV</td>
</tr>
<tr>
<td>Mao51</td>
<td>60</td>
<td>MVP + TCM</td>
<td>Astragalus, Chinese angelica, Atractylodes, Poria, polygonatum, ligustrum, paris [root], ornus, dried orangepeel</td>
<td>I-II</td>
</tr>
<tr>
<td>Shen26</td>
<td>80</td>
<td>NP + TCM</td>
<td>Stragalus, Atractylodes, Adenophora, Asparagus, Liriophe, almond, radix stemonae, trichosanthes rind, raw arisaema [root], Shizandra berry, Chinese sage, Oldenlandia diffusa, prunella, raw oyster shell, Bulbus Fritillariae</td>
<td>IIIb/IV</td>
</tr>
<tr>
<td>Shen DM71</td>
<td>72</td>
<td>NP + TCM</td>
<td>Astragalus, Atractylodes polygonatum, Adenophora, Liriophe, umbilicaria, ligustrum, babchi seed, Spatholobus stem, Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Sui23*</td>
<td>80</td>
<td>MVP + Astragalus combination</td>
<td>Lilium brownii, Rehmannia glutinosa, Scrophularia ningpoensis, Angelicae sinensis, Ophiopogonis japonicas, Paeonia lactiflora, Adenophora verticillata, Astragalus, Ligusticum lucidum, Paris polyphylla, Oldenlandia diffusa, Houttuynia cordata, Fritillaria cirrhosa, Cremastrea variabilis (with individualized additions)</td>
<td>II, III or IV</td>
</tr>
<tr>
<td>Sun71</td>
<td>74</td>
<td>CE-CAP/MVP/TC + Astragalus</td>
<td>Ganoderma lucidum, Pseudostellaria heterophylla, Coix lachryma, Atractyloids macrocephala, Astragalus, Lycium chinense,</td>
<td>III/IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage</td>
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<tr>
<td>-------</td>
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<td>------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Tian</td>
<td>40</td>
<td>NP + Fu Zhen Jie Du</td>
<td>Curcuma zeodoaria, Scolopendra subspinipes, Smilax glabra, Astragalus, Adenophora, Asparagus, Liriope, ligustrum, epimedium, Oldenlandia diffusa</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang</td>
<td>32</td>
<td>NP/MVP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang</td>
<td>98</td>
<td>NP + Ai Di injection</td>
<td>Adenophora verticillata, Asparagus cochin chinensis, Ophiopogonis japonics, Pseudostellaria heterophylla, Astragalus, Curcuma zeodoaria, Atractylodis macrocephala, C. aromatica, Paeonia rubra, Paeonia lactiflora, Oldenlandia diffusa, Scutellaria barbata</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang</td>
<td>93</td>
<td>MOP + Astragalus combination</td>
<td>Astragalus, Panax ginseng, Lilium brownii, Adenophora verticillata, Ophiopogonis japonics, Fritillaria cirrhosa, Morus alba, Trichosanthes kirilowii, Scutellaria baicalensis, Paris polyphylla, Scutellaria barbata, Solanum nigrum, Lepidium apetalum, Atractylodis macrocephala, Poria cocos, Phaseolus caracatus, Ziziphus jujube</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang</td>
<td>58</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Wang</td>
<td>46</td>
<td>GP/TP + TCM</td>
<td>Astragalus, polygonatum, umbilicaria, babchi seed, atractyloles</td>
<td>II-IV</td>
</tr>
<tr>
<td>Wang</td>
<td>78</td>
<td>NP + TCM</td>
<td>Astragalus, Campanumae pilosula, polygonatum, ligustrum, Spatholobus stem, ass hide glue (melt), Pinellia</td>
<td>II-IV</td>
</tr>
<tr>
<td>Weng</td>
<td>34</td>
<td>CAP + Astragalus combination</td>
<td>Codonopsis pilosulae, Astragalus, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Dioscorea opposita, Oldenlandia diffusa, Houttuynia cordata, Patrina villosa, Scutellaria barbata, Agrimonia pilosa, Ziziphus jujube</td>
<td>II-IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage †</td>
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<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Xie(^57)</td>
<td>60</td>
<td>NP + TCM</td>
<td>Ginseng, Atractyloides, Poria, Liquoric Root, Astragalus, Chinese angelica, Spatholobus stem, pyrosis [leaf], Barbed Skullcap Herb</td>
<td>III/IV</td>
</tr>
<tr>
<td>Xu(^46)</td>
<td>40</td>
<td>TP + Ke Liu Wan</td>
<td>Curcuma, mylabris, Gecko, Vietnamese Sophora Root, Leech, Ground Beetle, Astragalus</td>
<td>II-IV</td>
</tr>
<tr>
<td>Xu YQ(^99)</td>
<td>72</td>
<td>GP/TP + TCM</td>
<td>Astragalus, Adenophora, Liriope, apricot kernel, Thunberg Fritillary Bulb, Wild Buckwheat Rhizome, curcuma, Chinese Honeylocust Fruit, Coix Seed, Oldenlandia diffusa</td>
<td>IV</td>
</tr>
<tr>
<td>Xue(^27)</td>
<td>72</td>
<td>GP + TCM</td>
<td>Astragalus , pseudostellaria root,Atractyloides, Poria , Pinellia, dry orangepeel, mulferry root bark,rehmanniae vaporata , Heartleaf Houttuynia Herb, Oldenlandia diffusa</td>
<td>IIIb/IV</td>
</tr>
<tr>
<td>Yang(^40)</td>
<td>56</td>
<td>GP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Yang C(^53)</td>
<td>40</td>
<td>GP + Ke Liu Wan</td>
<td>Astragalus,mylabris, Leech</td>
<td>III/IV</td>
</tr>
<tr>
<td>Yu(^37)†</td>
<td>92</td>
<td>MAP + radiation + Astragalus combination</td>
<td>Astragalus, Pseudostellaria heterophylla, Poria cocos, Amomum xanthioides, Salvia miltiorrhiza, Paeonia rubra, Spatholobus suberectus, Schisandra chinensis, Glycyrrhiza uralensis (with individualized additions)</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhang(^63)</td>
<td>50</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhang(^62)</td>
<td>98</td>
<td>NP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhang(^80)</td>
<td>60</td>
<td>EP + Ai Di injection</td>
<td>Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabris cichoi</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhang(^44)</td>
<td>70</td>
<td>GP + Jian Pi Zi Yin</td>
<td>Astragalus, Atractyloides, Poria, cinnamomvine, Coix Seed, mix-fried licorice, pseudostellaria root, Adenophora, Liriope, ligustrum, dry toad's skin, Thunberg Fritillary Bulb, Buthus, notoginseng, curcuma</td>
<td>II-IV</td>
</tr>
<tr>
<td>Zhang WQ(^59)</td>
<td>60</td>
<td>MVP + Bu Qi Huo Xue</td>
<td>Astragalus, radix pseudostellariae, Atractyloides, amomum fruit, Poria, salvia, Spatholobus stem, Earthworm, Red Paeony Root, ligustrum, Oldenlandia diffusa, bulbus fritillariae, mix-fried licorice</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zhong(^83)</td>
<td>48</td>
<td>GP + Yi Fei Jian</td>
<td>Poria, Astragalus, Atractyloides, Pinellia, hovenia dulcis, sweetflag, hovenia dulcis, Platycodon Root, greater selaginella, dry toad's skin,</td>
<td>III/IV</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Protocol*</td>
<td>Ingredients</td>
<td>Stage †</td>
</tr>
<tr>
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</tr>
<tr>
<td>Zhou⁴²</td>
<td>60</td>
<td>NP + Fu Zhen Bu Xu</td>
<td>Wolfberry, ligustrum, epimedium, mix-fried turtle shell, Shizandra berry</td>
<td>II-IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Astragalus, Campanumaea pilosula, Poria, Atractyloides, dioscoreae, Chinese angelica, White Paeony Root, ass hide glue, Rehmannia, Wolfberry, ligustrum, semen psoraleae, cinnamon, Rehmannia, Liriop, Adenophora, dendrobium, Pinellia, dried orangepeel, Unibraet Fritillary Bulb, Liquoric Root</td>
<td></td>
</tr>
<tr>
<td>Zhou⁷³</td>
<td>63</td>
<td>CAP + Astragalus combination</td>
<td>Panax ginseng, Atractyloides macrocephala, Poria cocos, Astragalus, Polygonatum chinense, Ophiopogonis japonicis, Cordyceps chinensis, Lycium chinense, Ephedra sinica, Prunus armeniaca, Trionyx sinensis, Prunellae vulgaris, Oldenlandia diffusa, Scutellaria barbata, P. notoginseng</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zou²⁵</td>
<td>91</td>
<td>Cisplatin + Astragalus combination</td>
<td>Adenophora verticillata, Ophiopogonis japonicis, Pseudostellaria heterophylla, Paris polyphylla, Astragalus, Scutellaria barbata, Curcuma zeodoria, Atractyloides macrocephala, Paonia rubra, Paenia lactiflor, Oryza sativa, Hordeum vulgare, Massa fermenta, Crataegus pinnatifida, Cremastra variabilis, Curcuma aromatica, Citrus reticulata</td>
<td>III/IV</td>
</tr>
<tr>
<td>Zou⁵</td>
<td>60</td>
<td>MAP + Astragalus</td>
<td>Astragalus</td>
<td>III/IV</td>
</tr>
</tbody>
</table>


* In studies that included stage II patients, all patients received systemic therapy, and no patients received surgery.

† In studies in which patients received radiation in addition to chemotherapy, all patients in both groups received radiation and chemotherapy. The only difference between the two groups was whether they received *Astragalus*-based herbal medicine.
Traditional Chinese Medicines in the Treatment of Hepatocellular Cancers: A
Systematic Review and Meta-analysis

Ping Wu MB ChB, MSc (1)
Jean Jacques Dugoua ND, PhD (2)
Oghenowede Eyawo MPH (3)
Edward Mills PhD (3,4)

6) Shanghai Hospital #4, Shanghai, China
7) Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of
   Pharmacy, University of Toronto, Toronto, Canada
8) Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada
9) Faculty of Health Sciences, University of Ottawa, Ottawa, Canada
Abstract:

Background

Liver cancer is a common malignancy with a high mortality rate. Given the poor prognosis associated with this cancer, many patients seek additional therapies that may improve quality of life or survival. Several Traditional Chinese Medicines (TCM) have been evaluated in clinical trials, but little is known about them outside of China.

Methods

We searched independently and in duplicate 8 electronic databases, including 2 Chinese language databases, until February 2009. We included any randomized clinical trials (RCT) evaluating a TCM oral preparation for the treatment of hepatocellular cancers. We abstracted data on survival, tumor response, and performance scores. We conducted a random-effects meta-analysis and applied a meta-regression analysis.

Results

We included 45 RCTs (n= 3,236). All studies employed an active control group. In general, the reporting of methodological issues was poor. We analyzed data from 37 trials reporting on complete response effects score (Relative Risk [RR] of 1.26 (95 CI, 1.04-1.52, P=0.01, I²=0%, P=0.99). Products containing ginseng, astragalus and mylabris had a larger treatment effect (OR 1.34, 95% CI, 1.04-1.71, P=0.01) than the pooled broad estimate, also the case for astragalus-based treatments (OR 1.35, 95% CI, 1.001-1.80. P=0.048). We examined survival rates and pooled 15 studies reporting on 6 month outcomes (RR 1.10, 95% CI, 1.04-1.15, P=<0.0001, I²=0%, P=0.60). This effect was consistent at other prospective dates, including 12 months (22 trials, RR 1.26, 95% CI, 1.17-1.36, P=<0.0001, I²=7%, P=0.36), 24 months (15 trials, 1.72, 95% CI, 1.40-2.03, P=<0.0001, I²=0%, P=0.75); and, at 36 months (8 trials, RR 2.40, 95% CI, 1.65-3.49, P=<0.0001, I²=0%, P=0.62).
Conclusions

Our meta-analysis displays compelling evidence of effectiveness for hepatocellular cancers that should be evaluated in high-quality and transparent clinical trials.
**Introduction**

Worldwide, liver cancer is the fifth most common malignancy in men and the eighth in women\(^1\). According to the World Health Organization (WHO), liver cancer is a major health problem and its incidence is increasing\(^2\). In the United States alone, it is estimated that there will be 22,620 new cases and 18,160 deaths related to liver cancer in 2009\(^3\).

The major risk factor for liver cancer is the presence of cirrhosis of the liver, largely due to chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infection\(^4\). It is believed that the combined effects of these infections account for well over 80% of liver cancer cases worldwide\(^1\). Through HBV vaccines and screening of blood and blood products for HBV and HCV, primary liver cancer is the first human cancer largely amenable to prevention\(^1\).

With respect to treatment, the plan depends on a number of factors, including the extent of the disease, growth pattern of the tumour and hepatic functional reserve of the patient\(^5\). In cases of localized resectable liver tumours, standard treatment is surgical resection (partial hepatectomy) in patients without liver cirrhosis and surgical resection or liver transplantation in patients with liver cirrhosis\(^5\). In cases of localized non-resectable liver tumours, the standard treatment of total hepatectomy with liver transplantation is considered first followed by other options, including chemoembolization, percutaneous ethanol injection, radiofrequency ablation, inclusion in clinical trials or systemic chemotherapy (anthracyclines, cisplatin and 5-FU)\(^5\). Systematic chemotherapy, however, is reported to have a 10% response rate and no survival benefit\(^5\). In cases of advanced liver tumours, there is no established standard of care\(^5\).

Given the poor prognosis associated with some liver cancers and limited treatment options outside of surgery, patients may seek alternative treatments, including traditional Chinese medicine (TCM) products, alone or in combination with standard of care. The purpose of
this study is to systematically review and meta-analyze data from randomized clinical trials (RCTs) for evidence on the efficacy of TCM products in the treatment of liver cancer.

Methods:

Search strategy, trials selection, and data retrieval

To be eligible for inclusion in our systematic review, studies had to have enrolled adult patients (>18 years) with liver cancer. The patients had to be randomly allocated to an active TCM formulation treatment or a control group with either placebo or no treatment. In addition, any co-intervention had to be the same in both groups except for the TCM formulation. We excluded studies that reported only laboratory values rather than clinical responses. We also excluded direct comparisons of TCM formulations.


Three reviewers (PW, EM and HL) assessed eligibility based on the full text papers and conducted data extraction, independently, using a standard pre-piloted form. Disagreements were resolved by consensus or by a third reviewer. If the required information was not available in the published article, we obtained additional information in correspondence with the authors. We included all evaluated outcome measures including: disease stage, Karnofsky
performance (KP), the Child-Pugh score and the response evaluation criteria in solid tumors (RECIST). The response is categorized as complete response (CR), partial response (PR) outcomes, stable disease (SD), progressive disease (PD) and as CR + PR as a proportion for response rate (RR). We additionally examined survival rates by group according to 6, 12, 18, 24, 36 and 60-month survival rates, where reported.

In addition, we extracted data on trial quality, protocol, and outcomes assessed. We assessed quality through the reporting of the following criteria: sequence generation, allocation concealment, reporting of who was blinded, adequate descriptions of patient withdrawal, language of publication, and exposure to chemotherapy. We also noted the language in which the paper was written and the setting the studies were conducted. These criteria were not used for weighting covariates in the meta-analysis; instead, these were considered a priori explanations for study heterogeneity.

**Statistical analysis:**

We applied the Relative Risk and 95% Confidence Intervals as our primary effect measure in this analysis. For analysis examining response and survival, favourable results for the TCM intervention are in the direction greater than 1. In circumstances of zero outcome events in either arm of a trial, we used the Haldane method and added 1 to each arm, as suggested by Sheehan. We first pooled studies on all interventions versus all controls using the DerSimonian-Laird random effects method. This method recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. We calculated the $I^2$ statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.
Forest plots are displayed for the primary analysis, showing individual study effect measures with 95% CIs and the overall DerSimonian-Laird pooled estimate. We conducted a meta-regression analysis using the unrestricted maximum likelihood method to determine if the \textit{a priori} covariates of TCM formulation yielded differing effects. We examined publication bias visually and through the Begg-Mazumdar, Egger, and Horbold-Egger tests. We calculated the optimal information size (OIS) required to determine adequate power across trials. We used Stats Direct and Comprehensive Meta-Analysis (Version 2) for all statistical procedures. All p-values are 2-sided and a p-value <0.05 was considered significant. PW and EM conducted the analysis.

\textbf{Results:}

Our extensive searching yielded 130 titles and/or abstracts, of which 54 were found likely to be relevant. Nine of the full text articles reviewed were excluded for one of two reasons: 1) either the study was not randomized; 2) TCM was the control intervention. 3 study was duplicated.

In total, 45 publications \textsuperscript{9-53} containing independent data fit the criteria for inclusion. Figure 1 details the literature retrieval process used during our searches and the rationales for exclusion leading to the final selection. Among the final 45 studies, \textsuperscript{44} 9-14,16-53 were published in Chinese languages and \textsuperscript{15} was published in English. All the studies were conducted in China.

\textbf{Characteristics of included studies}

The 45 RCTs included 3,236 patients, 1,682 in the treatment groups and 1,554 in the control groups (See Table 1 and 2). Most trials were small and the median intervention group size was 32 (interquartile range [IQR] 30-42) and control group size is 31 (IQR 30-38). The
majority of trials (24)9, 12, 13, 15-18, 25, 27, 29, 30, 32, 34-36, 40, 46, 47, 49-54 included patients with stage II or more advanced cancers. Table 1 displays the study characteristics and formulations along with the TCM philosophy for the preparation. All studies employed transcatheter arterial chemoembolization (TACE) as adjunct therapy. No placebo was used as the control group in any study.

**TCM Interventions**

The TCM interventions identified in this study were principally combinations of different herbal medicines or animal/insect extracts (Table 2). A brief outline on the oncologic and immunologic pharmacology of the most commonly used ingredients is presented below.

*Astragalus*

Astragalus appears to have a number of immunomodulatory properties55-57. Astragalus appears to have anti-tumour activity where its potentiates LAK cell activity *in vitro* when used in combination with IL-258. Astragalus appears to restore *In vitro* T-cell function, which is suppressed in cancer patients59.

*Panax ginseng*

*Panax ginseng* and its chemical constituents were found to have inhibitory effects on putative carcinogenesis mechanisms, e.g., cell proliferation and apoptosis, immunosurveillance and angiogenesis60. Ginsenosides from *Panax ginseng* have been shown to inhibit tumor cell invasion and to suppress sister chromatid exchanges in human lymphocytes61.

*Toad skin secretions (bufotoxin)*

The toad skin secretion bufalin was found to induce apoptosis in human-leukemia cells by altering expression of apoptotic genes c-myc and bcl-262. Other toad skin secretions like 3-formyloxyresibufogenin, 19-oxobufalin, 19-oxodesacetylcinobufagin, 6-hydroxycinobufagin
and 1-hydroxybufalin were found to exert inhibitory effects on KB, HL-60 and MH-60 cancer cell lines\textsuperscript{63}.

\textit{Beetle extracts (Mylabris)}

An extract from \textit{Mylabris phalerata}, the dried body of the Chinese blister beetle, was shown to have anti-cancer activity via inducing cancer cell apoptosis and was associated with little toxicity\textsuperscript{64}.

\textit{Atractylodes}

Atractylodes appears to have anticancer activity by inducing apoptosis and cytotoxic effects against leukemia and other cancer cell lines\textsuperscript{65}.

\textit{Bupleurum}

Saikosaponins from \textit{Bupleurum falcatum} were shown to exhibit potent anti-cell adhesive activity on solid tumour cells and to have strong hemolytic action\textsuperscript{66}.

\textit{Curcuma}

\textit{Curcuma longa} may have immunostimulatory activity\textsuperscript{67}.

\textbf{Meta-analysis.}

\textbf{Complete Response}

We analyzed data from 37 trials\textsuperscript{10, 12, 13, 15-18, 20, 21, 23, 25-30, 32, 33, 35, 36, 38-41, 44-54, 68, 69} reporting on RECIST CR score. Our pooled analysis indicates an RR of 1.26 (95 CI, 1.04-1.52, P=0.01, $I^2=0\%$, $P=0.99$). See figure 2. Applying meta-regression, we found that products containing ginseng, astragalus and mylabris had a larger treatment effect (OR 1.34, 95\% CI, 1.04-1.71, $P=0.01$) than the pooled broad estimate and that any product containing astragalus also had this effect (OR 1.35, 95\% CI, 1.001-1.80. $P=0.048$).
Partial response

We pooled data from 37 trials reporting on PR between groups. The pooled RR is 1.27 (95% CI, 1.17-1.38, P=<0.0001, I²=0%, P=0.99, See Figure 3). When we examined if differential effects existed across specific formulations, we found that studies using bufotoxin demonstrated increased effects (OR 1.25, 95% CI, 1.15-1.37, P=<0.0001), as did studies using ginseng, astragalus and mylabris (OR 1.27, 95% CI, 1.16-1.39, P=<0.0001) and any product using astragalus (OR 1.27, 1.13-1.42, P=<0.0001).

Stable disease

We pooled data from 37 trials reporting on stable disease between groups at study conclusion. The pooled RR is 1.03 (95% CI, 0.93-1.15, P=0.47, I²=10%, P=0.29, see figure 4). When we examined the effects of different preparations we did not show an effect with bufotoxin (OR 1.04, 95% CI, 0.95-1.15, P=0.35), with ginseng, astragalus and mylabris (OR 1.04, 95% CI, 0.95-1.14, P=0.40) or any product using astragalus (OR 1.02, 1.02-1.13, P=0.63).

Progressive disease

We pooled data from 37 trials reporting on progressive disease among patients. We found an inflated progressive disease rate in the control groups (RR 0.54, 95% CI, 0.45-0.64, P=<0.0001, I²=0%, P=0.66, see figure 5). Studies utilizing bufotoxin had a decreased risk (OR 0.54, 95% CI, 0.46 to -0.65, P=<0.0001), this was also the case with studies using ginseng, astragalus and mylabris (0.54, 95% CI, -0.46 to -0.66, P=<0.0001) and with studies using any form of astragalus (OR 0.57, 95% CI, 0.46 to -0.70, P=<0.0001).
Survival rates

We examined survival rates and pooled 15 studies\(^{12, 17, 25, 26, 28, 29, 33, 36, 42, 44, 46, 50, 54, 69, 70}\) reporting on 6 month outcomes (RR 1.10, 95% CI, 1.04-1.15, P=<0.0001, \(I^2=0\\%\), P=0.60). This effect was consistent at other prospective dates, including 12 months (22 trials\(^{9, 12, 17, 20, 25, 29, 31, 33, 35, 36, 41, 42, 44, 46, 47, 50, 54, 69, 70}\), RR 1.26, 95% CI, 1.17-1.36, P=<0.0001, \(I^2=7\%\), P=0.36, See figure 6); 18 months (4 trials\(^{9, 26, 28, 52}\), RR 1.71, 95% CI, 1.002-2.91, P=0.049, \(I^2=70\%\), P=0.009); 24 months (15 trials\(^{17, 20, 26-28, 31, 33, 36, 41, 42, 46, 52, 54, 69, 70}\), 1.72, 95% CI, 1.40-2.03, P=<0.0001, \(I^2=0\%\), P=0.75); and, at 36 months (8 trials\(^{27, 31, 33-35, 42, 47, 69}\), RR 2.40, 95% CI, 1.65-3.49, P=<0.0001, \(I^2=0\%\), P=0.62). We applied meta-regression on the 12 month survival and found increased effect with bufotoxin (OR 1.22, 95% CI, 1.13-1.32, P=<0.0001) and with products containing ginseng, astragalus and mylabris (OR 1.24, 95% CI, 1.16-1.33, P=<0.0001) and astragalus alone (OR 1.28, 95% CI, 1.15-1.40, P=<0.0001).

Symptom improvement

Several studies reported on improvement of symptoms. In particular, 6 studies\(^{13, 15, 23, 29, 44, 68}\) reported on abdominal pain improvements favouring TCM approaches (RR 1.50, 95% CI, 1.09-2.07, P=0.013, \(I^2=44\%\), P=0.11). Abdominal distension did not improve among TCM recipients in 5 reported trials\(^{8, 18, 24, 39, 50}\) (RR 1.26, 95% CI, 0.96-1.64, P=0.09, \(I^2=4\%\), P=0.38). Fatigue significantly improved in 4 reported trials\(^{8, 18, 24, 39}\) (RR 1.54, 95% CI, 1.17-2.01, P=0.001, \(I^2=0\%\), P=0.87), and appetite improved in 4 reported trials\(^{8, 18, 24, 39}\) (RR 1.53, 95% CI, 1.14-2.05, P=0.004, \(I^2=0\%\), P=0.45).
Optimal Information Size (OIS)

Almost all trials included in our analysis were small. We applied OIS based on the event rate in the intervention and control arms for the PR outcome. We found an event rate of 0.42 in the intervention arms and an event rate of 0.33 in the control arms. When applying 80% power and a two-tailed 5% alpha, we identify that we require at least 906 participants in our meta-analysis.

Publication bias

We assessed publication bias visually with a funnel plot (see figure 4) and applied several statistical tests to determine the likelihood of publication bias. We found no evidence when applying the Begg-Mazumdar test (P=0.14), Egger’s test (P=0.80) or Horbold-Egger’s test (P=0.89). We also imputed the number of studies that were likely missing, but the resulting number was unconcerning (n=2) and was unlikely to change the effect estimate.

Discussion

We found consistent effects of traditional Chinese medicines when combined with TACE versus TACE alone. The majority of studies included in our analysis were small or of moderate size and none can provide definitive answers on treatment options, although compelling results related to bufotoxin, astragalus and products containing ginseng, astragalus and mylabris warrant further examination. Our study also highlights the utility that searching in non-English languages may have on identifying potentially useful new interventions for common diseases.
Strengths of our study include our extensive searches of literature in both English and in Chinese languages, and using Chinese language databases for our search. Two of us (PW, HL) understand and read Mandarin and Cantonese, along with English, thus allowing searches across several languages. We applied a broad criteria for pooling studies. We included any TCM formulation and then conducted a meta-regression analysis to determine if specific preparation yielded differing effects over the broad group, and in several cases did.

Limitations of our study include the underlying concern about the quality of the included studies. As we highlight, the majority of studies were small, with typically 30 participants per arm. Meta-analysis aims to overcome issues of power through pooling, thus increasing sample size and power. We applied an OIS on the overall event rate of partial response and found that a pooled sample size of 1,108 provided sufficient evidence of an effect. This did not apply to specific formulations. We further assessed issues of methodological rigour as two major concerns with Chinese-based clinical trials. Firstly, is that only positive trials are published in Chinese medical journals, and second, is that some trials reported as randomized are, in fact, not randomized. A recent evaluation by Wu et al. found that many studies labelled as RCTs with Chinese journals were, in fact, not randomized. In our own experience, we recognize many Chinese clinical trialists have not been exposed to appropriate clinical epidemiology training. We examined publication bias through both visual inspection of the funnel plot on the primary outcome (PR) and through statistical tests, but were unable to identify publication bias. However, funnel plots cannot rule out publication bias and we remain cautious.
From a clinical standpoint, the results of this study are very encouraging but should be implemented with caution. The average clinician will be reassured that TCM interventions, both herbal-based and animal/insect-based, were safely combined with chemotherapy. The average clinician, however, likely will not scrutinize the results of this study using evidence-based principles and may implement our findings into practice due to the overwhelming positive response in our meta-analysis. Given this tendency, the results from this study should be carefully disseminated to the medical community with the caveat that although promising, our findings need to be confirmed via a RCT conducted in a Western academic setting.

Our study may prove useful for a number of reasons. Firstly, there is reason to further examine the evidence of several of the interventions included in our analysis. Other investigators have examined the role of herbal medicines and TCM interventions for hepatocellular cancers, lung cancers and hepatitis and found compelling evidence in humans.\textsuperscript{72-74} However, perhaps a far more important finding from our analysis and approach is the role that searching for clinical trials in non-English languages may play in drug discovery. Important first line drugs, such as artemisinin-based therapies for malaria, have been discovered through searching existing trials in non-English languages.\textsuperscript{75}

Our study builds on the findings of others about the heterogeneous quality of randomized trials from China. In our own experience in China, we have doubts that many methodological features attributed to randomized trials, were in fact conducted. A previous analysis, by Vickers et al, found that most trials conducted in China were reported as positive,\textsuperscript{76} a finding our analysis also supports\textsuperscript{8}. While several explanations for this
phenomenon exist, a likely explanation is the slow uptake of evidence-based medicine and clinical trials methodology in academic research centres. With the opening of the Chinese Cochrane Centre, we hope that clinical epidemiology will receive considerably more attention.

In conclusion, our study provides important inferences about new potential therapeutic options for hepatocellular cancers. While these finds are compelling, there is a need for confirmation of these studies in well-conducted RCTs conducted in Western settings. Until such time, potentially useful interventions cannot be wholly recommended based on evidence alone.

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Conflict of interest: The authors declare no conflict of interest.

Figure Legend:
Figure 1. Flow diagram of included studies.
Figure 2. Forest-plot of complete response.
Figure 3. Forest plot of partial response.
Figure 4. Forest plot of stabilized disease.
Figure 5. Forest plot of progressive disease.
Figure 6. Forest plot of 12-months survival.
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restoration of local xenogeneic graft-versus-host reaction in cancer patients by fractionated
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Figure 1. Flow diagram of included studies.
Figure 2. Forest-plot of complete response.
Figure 3. Forest plot of partial response.

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[Forest plot image]

Favours controls  Favours TCM
Figure 4. Forest plot of stabilized disease.

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Figure 5. Forest plot of progressive disease.
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Table 2: Ingredients and philosophy related to each study

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<thead>
<tr>
<th>Author</th>
<th>TCM in Tr.Group</th>
<th>Ingredients</th>
<th>TCM philosophy</th>
</tr>
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<tbody>
<tr>
<td>Lin YZ 22</td>
<td>Shen Tao Ruan Gan Bolus</td>
<td>Artemisia capillaris, Hedyotis diffusa Wild, Scutellaria barbata, Rhizoma Curcuma, Peach Kernel, Angelica Sinensis, salvia, white ginseng, Poria cocos, Tortoise Plastron</td>
<td>supplement Qi, strengthening spleen, replenishing blood, blood-activating and stasis-dissolving, clearing heat and removing dampness and detoxification</td>
</tr>
<tr>
<td>Tan XZ 20</td>
<td>Ai Yi Shu injection</td>
<td>Disodium Cantharidine Injectio</td>
<td>breaking stagnant and eliminating blood stasis; attacking toxin and eliminating and resolving stagnation and masses</td>
</tr>
<tr>
<td>Wu XD 30</td>
<td>Hu Gan Ruan Jian Fang</td>
<td>radix codonopsis, Astragalus, poria cocos, Hedyotis diffusa Wild, bear grass, Centipede, Atractylodes, Curcuma, Bupleurum, CARAPAX TRIONYCIS</td>
<td>supplement Qi, strengthening spleen, replenishing blood, eliminate and resolve stagnation and masses, nourishing kidney, supporting the normal and raising of the origin</td>
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<tr>
<td>Yu QT 41</td>
<td>Chinese toad bufotoxin injection</td>
<td>Chinese toad bufotoxin injection</td>
<td>detoxification, detumescence and analgesia, eliminate and resolve stagnation and masses</td>
</tr>
<tr>
<td>Zhang YF 46</td>
<td>Chinese herbal compound</td>
<td>Bupleurum, Astragalus, red radix paeoniae alba, Atractylodes, Magnolia, Szechwan Chinaberry Fruit, Membrane of Chicken Gizzard, wolfberry fruit.</td>
<td>relieving the depressed liver, invigorating spleen and stomach, nourishing liver and kidney, eliminate and resolve stagnation and masses</td>
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<tr>
<td>Li WH 20</td>
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<td>Chinese toad bufotoxin injection</td>
<td>detoxification, detumescence and analgesia, eliminate and resolve stagnation and masses</td>
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<tr>
<td>Zhao XW 49</td>
<td>Shen Qi capsule</td>
<td>Angelica Sinensis, lanceolata, Schisandra Chinensis, Artemisia capillaris, Astragalus, medofenoxate Extra, milk thistle</td>
<td>supplement Qi, nourishing Yin and liver, invigorating spleen and kidney,</td>
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<td>American ginseng, CARAPAX TRIONYCIS, Zedoary, rhizome spangani, tortoise plastron, White Peony Root, Astragalus</td>
<td>supplement Qi, nourishing Yin and liver, invigorating spleen and kidney, eliminate and resolve stagnation and masses, relieving pain</td>
</tr>
<tr>
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<td>Jew Ear Parasitized</td>
<td>strengthening vital, activating blood and eliminating broomsymptom</td>
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<tr>
<td>Xu ZW 38</td>
<td>modified six nobles decoction</td>
<td>ginseng, Atractylodes, Poria Cocos, Glycyrrhiza, Tangerine Peel, Pinellia ternate, Perilla, Radix auclladiae, Citrus Aurantium, areca peel</td>
<td>supplement Qi and invigorating spleen; eliminating dampness to reducephlegm</td>
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<tr>
<td>Wang RP 29</td>
<td>Gan Ji grain</td>
<td>Astragalus, CARAPAX TRIONYCIS, lanceolata, Coix seed, White Peony Root, Atractylodes, Zedoary, barbed skullcap</td>
<td>supplement Qi and eliminate and resolve stagnation and masses</td>
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<td>clearing heat, detoxification, eliminate and resolve stagnation and masses</td>
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<td>De Li Shen injection</td>
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<td>Ingredients</td>
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<td>Cao MR</td>
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<td>stagnation and masses</td>
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<td>detoxification, detumescence and analgesia, eliminate and resolve stagnation and masses</td>
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<td>Liu XL</td>
<td>Yan Shu injection</td>
<td>Sophora flavescentis, white Poraria Cocos</td>
<td>clearing heat and detoxification, removing dampness;</td>
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<td>Wu WG</td>
<td>pingxiao capsule</td>
<td>Curcuma Longa, Alumen, Potassium nitrate, nux vomica, Agrimony, etc</td>
<td>clearing heat and detoxification; eliminate and resolve stagnation and masses, Strengthening Healthy Qi</td>
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<tr>
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<td>Lanceolata, Astragalus, Coix seed, Bupleurum, Common Yam Rhizome, Reynoutria, Akebia Stem</td>
<td>invigorating spleen and liver; clearing heat removing dampness;</td>
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<td>Coix seed oil injection</td>
<td>strengthening spleen, invigorating the lung, clearing heat and removing dampness;</td>
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<td>AC-III injection</td>
<td>Ginseng, Arsenolite, calomelas, muskmelo pedicel</td>
<td>Strengthening Healthy Qi, removing blood stasis, toxicity and excessive pathogenic factors</td>
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<td>Pei Ren Gu Yuan anti-cancer capsule</td>
<td>Ginseng, Corydalis, Astragalus, Salvia, balsam pear, Mythic Fungus, Hedyotis diffusa Wild, Angelica, Algae, acanthopanax senticosus, Scutellaria barbara</td>
<td>strengthening vitals; eliminate and resolve stagnation and masses, relieving pain; promoting digestion and anchoring mind; replenishing qi and blood; clearing heat and detoxification; promoting urination and dehumidification;</td>
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<td>Radix Adenophora, Radix oshionopsis, radix ophiopogonis, angelica, radix rhemanniae, polygonus, solanum nigrum, prunella vulgaris, Spreading Hedvotis Herb, etc</td>
<td>clearing heat and nourishing Yin, strengthening spleen and removing dampness, replenishing qi and blood, cooling blood to stop bleeding.</td>
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<tr>
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<td>Ginseng, Astragalus, Scorpion, atractylodes, cyperus rotundus, placenta hominis, Scutellaria barbata</td>
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<td>dark plum, ginseng, atractylodes, CARAPAX TRIONYCIS, Sophora flavescens, Poraria Cocos, Coix seed, Dogwood Fruit, Scutellaria barbata</td>
<td>strengthening body resistance, eliminate and resolve stagnation and detoxification</td>
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<td>Shaxian Granula</td>
<td>Hawthorn, Agrimony, American Ginseng, Zedoary, etc</td>
<td>replenishing blood, eliminate and resolve stagnation and masses,</td>
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<td>TCM in Tr.Group</td>
<td>Ingredients</td>
<td>TCM philosophy</td>
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<td>strengthening spleen and replenishing kidney, clearing away heat and detoxification, soft the hard lumps and dissipate phlegm</td>
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<td>strengthening spleen and supplementing Qi, blood-activating and stasis-dissolving</td>
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