EFFECTS OF NORTH AMERICAN GINSENG
(Panax quinquefolius L.)
ON
POSTPRANDIAL GLYCEMIA IN NORMAL HUMANS

by

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A thesis submitted in conformity with the requirements
for the degree of M.Sc.
Graduate Department of Nutritional Sciences
University of Toronto

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ABSTRACT

To investigate the effects of North American ginseng (Panax quinquefolius L.) powder on reducing postprandial glycemia, a glucose challenge of 25 g carbohydrate was used. Capillary blood was collected at fasting, 15, 30, 45, 60, and 90 minutes after initial consumption of glucose challenge.

Ginseng powder (3 g, 6 g and 9 g) with glucose challenge, had no significant effect on blood glucose when compared to glucose alone in healthy individuals (4 males, 4 females). However, when 3 g and 6 g of ginseng powder were ingested 40 or 80 minutes prior to glucose drink, lower glycemic responses (4 males, 2 females, p < 0.05) were observed. Lower glycemic response also resulted from 9 g Panax quinquefolius L. ingested at either 40 minutes (p < 0.01), 80 minutes (p < 0.01), or 120 minutes (p < 0.05) prior to glucose challenge. This glycemic response was not dose dependent.

It was concluded that Panax quinquefolius L. lowers postprandial glycemia at levels of 3 g, 6 g, 9 g, and possibly at lower doses, when taken prior to glucose challenge.
In loving memory of my mother, Marie
First, I would like to thank my supervisor, Dr. V. Vuksan, for his support and encouragement. Without his insightful supervision and encouragement, this work would not have been accomplished. To Dr. T.M.S. Wolever, your invaluable guidance and suggestions were greatly appreciated. I would also like to thank Dr. T. Francis for his continued support and assistance throughout my program. Special thanks to Dr. A.V. Rao for being on my Advisory Committee, Drs. D.J.A. Jenkins and S.C. Cunnane for serving on my Examination Committee, and Dr. T. Heim for being my Appraiser. I am also grateful to Dr. L.U. Thompson for all her guidance over the years.

I am indebted to my friends who graciously participated in my research experiments. Without their commitment, this study would never have been completed. Sincere thanks to George Yeung for all his encouragement, advice and statistical help, and Evelyn and Brenda for all their help and fun during my studies. I am also grateful to the staff of the graduate department, in particular, Brenda Rak, for keeping me up to date.

Thanks to Atkins Farm Limited and Chai-Na-Ta Corporation for their generous contribution of ginseng capsules and research information.

Finally, my deepest thanks to my family for their unconditional love and support. To my father and Auntie Phyllis, your patience and care are greatly appreciated. To Tina and Clarence, thanks for putting up with me even when I was frustrated. To Christina, thanks for being inexhaustibly loving and supportive throughout.
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ABBREVIATIONS

% Percent
AUC Incremental blood glucose area under curve
BMI Body mass index
DIOL Protopanaxadiol
Fig Figure
g Grams
GS Ginsenosides
IDDDM Insulin-dependent diabetes mellitus
kg Kilograms
min Minutes
mL Milli-Litre
mmol/L Milli-mole per Litre
NIDDM Non-insulin dependent diabetes mellitus
P. ginseng Panax ginseng C.A. Meyer
P. japonicus Panax japonicus C.A. Meyer
P. quinquefolius Panax quinquefolius L.
SE Standard error of mean
T. CHO Total carbohydrate
TCM Traditional Chinese medicine
TRIOL Protopanaxatriol

x
CHAPTER ONE

INTRODUCTION

AND

LITERATURE REVIEW
1.1 Introduction

The value of ginseng in promoting overall body health has long been recognized by the Chinese, who claim to have been using ginseng for 5,000 years [Bloomfield, 1987]. The first known reference appeared in a manuscript from the third century BC, suggesting that there exists a very long history of ginseng by humans consumption [Bloomfield, 1987]. In fact, it was recorded in the first official Chinese pharmacopoeia, *Shen Nung Pen Tsao*, published almost 2,000 years ago. However, *Shen Nung Pen Tsao* was later revised in fifth century AD and few additions were made which included using ginseng to treat thirst and polyuria due to diabetes, to reduce swelling and inflammation, and to increase memory [Bloomfield, 1987]. Despite its long history of medicinal use, ginseng health beneficial claims are generally based upon anecdotal evidence. It has only been over the past 20 years or so that some of the many claims are examined scientificaly.

Ginseng is the common name of mainly two species of *Panax* herbs, belonging to the family of *Araliaceae* [Li and Li, 1973]. North American ginseng is botanically known as *Panax quinquefolius* L. (*P. quinquefolius*), while the more extensively studied root, Chinese or Korean ginseng, is called either *Panax schinseng* Nees or *Panax ginseng* C.A. Meyer (*P. ginseng*) [Fulder, 1993]. The latter name is the more commonly used name for Oriental ginseng today.

There are various compounds which are believed to be biologically active in the *Panax* species. Triterpenoid glycosides or saponins termed ginsenosides (GS) by Japanese
more studied ginseng components. Chemical analysis shows that both *P. quinquefolius* and *P. ginseng* contain similar types of GS with the only difference being their respective quantities (Table 1.1). In addition, they also have very comparable nutrient profiles (Table 1.2). Other active constituents include polysaccharides, some of which are termed panaxans; peptides, a carboxylic acid, adenosine, and flavonoids [Konno et al., 1984; Tomoda et al., 1984; Konno et al., 1985; Oshima et al., 1985; Zhu et al., 1989; Yang et al., 1990; Yang and Wang, 1991]. However, these compounds have only been confirmed in Oriental ginseng.

It has been reported numerous times that ginseng components extracted from *P. ginseng* have hypoglycemic activity in diabetic rodents [Kimura et al., 1981a; Kimura et al., 1981b; Kimura and Suzuki, 1985; Waki et al., 1982; Yokozawa et al., 1985; Yang et al., 1990; Yang and Wang, 1991; Wang et al., 1990a; 1990b]. However, the attributes of ginseng that impact diabetic control in humans are not very well elucidated. Nevertheless, recent findings by Sotaniemi et al. [1995] indicate that Oriental ginseng extract may be a beneficial therapeutic adjunct in the management of non-insulin dependent diabetes mellitus (NIDDM).

Since *P. quinquefolius* and *P. ginseng* have similar nutrient profiles, contain several commonly considered active constituents in common, and Oriental ginseng components have been demonstrated to be beneficial in diabetic humans and animals, it is hypothesized that North American ginseng also possesses similar physiological activities as its Asian cousin. Furthermore, the majority of ginseng research has been conducted on
The purpose of this study is to investigate the efficacy of *P. quinquefolius* powder ground from ginseng root hair in lowering postprandial glycemia in humans. Since the dose and method of administration have not been specified, the results from this study allow for the determination of the optimal time and dose of administration of North American ginseng. In addition, the results also give light to designing further clinical studies with NIDDM patients.
<table>
<thead>
<tr>
<th>Type</th>
<th>P. ginseng (%)</th>
<th>P. quinquefolius (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protopanaxadiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rp1</td>
<td>0.37</td>
<td>1.84</td>
</tr>
<tr>
<td>Rp2</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>Rp3</td>
<td>0.13</td>
<td>0.31</td>
</tr>
<tr>
<td>Rc</td>
<td>0.13</td>
<td>0.45</td>
</tr>
<tr>
<td>Rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protopanaxatriol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rc</td>
<td>0.20</td>
<td>1.0</td>
</tr>
<tr>
<td>Rg1</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>Rg2</td>
<td>0.02</td>
<td>0.008</td>
</tr>
<tr>
<td>Oleanolic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rho</td>
<td>0.04</td>
<td>0.07</td>
</tr>
</tbody>
</table>

1 Sprecher, 1987
Table 1.2 Nutrient Profiles of *P. quinquefolius* and *P. ginseng*

<table>
<thead>
<tr>
<th>Types of Ginseng (per 100g)</th>
<th><em>P. quinquefolius</em>¹</th>
<th><em>P. ginseng</em>²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>371.2</td>
<td>345.4</td>
</tr>
<tr>
<td>T. CHO (g)</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>

¹ Samples supplied by Chai-Na-Ta Corp. and Atkins Farm Ltd. [JR Laboratories Inc., BC, 1997; Industrial Lab of Canada Inc., Ont., 1997]

² Samples supplied by Atkins Farm Ltd. [Industrial Lab of Canada Inc., Ont., 1997]
1.2.1 History of ginseng

1.2.1.1 Description

The term, ginseng, is often applied to two Panax species of the Araliaceae family; *Panax quinquefolius* L. and *Panax ginseng* C.A. Meyer [Li and Li, 1973]. While *Panax* is derived from the Greek word, *pan-axos*, which literally means all-healing [Owen, 1980; Fulder, 1993], ginseng means ‘essence of the earth in the form of a man’ [Graham, 1966].

North American ginseng is botanically known as *Panax quinquefolius* L. (*P. quinquefolius*), where L denotes Linnaeus who named the plant. Oriental ginseng (Chinese or Korean ginseng), on the other hand, was originally named *Panax schinseng* Nees by Nees van Esenbeck which was later changed to *Panax ginseng* C.A. Meyer (*P. ginseng*) by Carl Anton Meyer in 1842 [Fulder, 1993]. Today, the Oriental variety is commonly referred to as *Panax ginseng* C.A. Meyer.

1.2.1.2 North American Ginseng (*Panax quinquefolius* L.) trade

*P. quinquefolius* is native to the rich, rocky, shaded, cool slopes of eastern North America, from Quebec to Manitoba of Canada, south to northern Florida, Alabama, and Oklahoma of the United States [Foster, 1993]. Ginseng roots are herbaceous perennials which have historically been used as a medicinal plant and a trading commodity by all native populations in the areas where it was grown [Oliver, 1990].

North American ginseng (*P. quinquefolius*) was first discovered in Quebec in 1704 by Michael Sarrasin, the King’s Physician to Canada [Hellyer, 1984]. The root was later found again by Father Lafitau, a Jesuit Missionary, near Sault Ste Louis, Quebec in 1715.
North American ginseng root was first exported from Canada to China by Father Jartoux [Goldstein, 1975]. By 1770's, it was recorded that an average of 140,000 pounds ginseng roots native to North America was exported each year [Foster, 1991]. However, near the turn of the eighteenth and nineteenth centuries, the early substantial profit gained from trading North American ginseng with China resulted in large quantity of ginseng being over-harvested and improperly dried in a short period of time [Hellyer, 1984]. As a result, the roots were shipped in such bad condition that it became unacceptable to the Chinese which led to an enormous decline in ginseng trade with China. Exports continued to decrease as wild ginseng became scarce with the possibility of extinction [Hellyer, 1984]. This situation prompted protective measures from the United States government and in 1890 Ontario government adopted the guidelines and prohibited ginseng gathering between January and September [Hellyer, 1984].

Cultivation of North American ginseng was first attempted in 1890 by George Stanton at Fabius, New York by transplanting wild ginseng. Soon after this, many pamphlets were published to provide information on the techniques of growing and drying ginseng roots [Hellyer, 1984]. However, the ginseng industry suffered yet another fall during the depression in 1929. It was not until 1940 before export resumed [Hellyer, 1984]. Today, *P. quinquefolius* has established itself as a major Canadian cash crop [Thomas, 1996]. In 1995, there were approximately 250 ginseng growers producing 2.1 million pounds of dried ginseng root, valued at $40 a pound. The total crop value was $84 million. The major market for the crop remains Asia [Thomas, 1996].
1.2.1.3 **Chinese perception on North American ginseng**

Chinese are the greatest ginseng consumers in the world [Schreiner, 1995]. They favour *P. quinquefolius* for several reasons. First, when the North American root was initially exported to China, wild *P. ginseng* had already become extremely scarce. Asians believe that United States manufactured or produced goods to be of superior quality. The taste of *P. quinquefolius* is sweeter than its Asian variety. In addition, *P. quinquefolius* and *P. ginseng* are considered to possess distinct medicinal properties. *P. quinquefolius* is considered more *yin* in TCM which means that it is good to reduce heat for cooling of the respiratory or digestive systems. *P. ginseng*, on the other hand, is more *yang* and is a heat-raising or stimulating tonic for the blood or circulatory system. As a result, *P. quinquefolius* is preferred by Asians as it is a cold or mild tonic that will reduce “heat” in the system, while acting as a general tonic.

1.2.1.4 **History of North American ginseng use**

The use of *P. quinquefolius* by native groups was not very well documented. However, it was one of the five most important medicines among the Seneca Indians, primarily used by the elderly. Crow Indians used it to induce childbirth without suffering [Goldstein, 1975]. The Oklahoma Seminole used the root to cure nosebleed and treat shortness of breath [Howard, 1984]. Penobscots drank the water extract of the root to increase fertility in women [Speck, 1915]. Although Ojibwe had not been observed to use the root, they harvested it for sale.
1.2.1.5 Oriental ginseng: a traditional perspective

Chinese or Korean ginseng (*P. ginseng*) is the most popular *Panax* species and has been investigated substantially more than its North American cousin. This variety of ginseng has been used for 5,000 years in the Orient as a tonic, prophylactic agent and ‘restorative’ [Goldstein, 1975; Hu, 1977; Bloomfield, 1987]. In fact, it has been recorded in the first Chinese pharmacopoeia, *Shen Nung Pen Tsao*, published almost 2,000 years ago that *P. ginseng* ‘soothes base emotions, safeguards the soul, drives out fear, expels evil influences, brightens the eye, opens up the heart, increases the spirit, and if taken over a long period of time, prolongs life’ [Bloomfield, 1987]. In traditional Chinese medicine (TCM), this explanation indicates that ginseng affects liver and kidney functions, heart and blood circulation, and treats diseases associated with exposure to “cold” or *yin* conditions, such as body aches and pains, muscular contraction, diarrhea, nausea, indigestion, and influenza [Bloomfield, 1987]. However, *Shen Nung Pen Tsao*, was later revised in fifth century AD by T’ao Hung-ching. Additional health conditions were attributed to Oriental ginseng, including treatment of thirst and polyuria due to diabetes, reducing swelling and inflammation, and increasing memory capacity [Bloomfield, 1987].

In 1552 AD, a famous herbalist, Li Shih-chen (1518–1593), compiled all the knowledge contained in thousand of volumes of herbal knowledge in China into a 52-volume pharmacopoeia called *Pen Tsao Kang Mu* [Bloomfield, 1987] in which ginseng was described in detail [Li et al., 1973]. This collection was completed by Li’s son after his death and was published for the first time in 1578. In fact, it is still in print today and
ingredients used in medical treatments – herbs, roots, minerals, and animal products – but also over 8,000 prescriptions [Bloomfield, 1987].

1.2.1.6 Oriental ginseng: a modern perspective

Due to its long history of use, P. ginseng has been the focus of most ginseng scientific investigations. As a consequence, Oriental ginseng is the most studied Panax species. Over the past 20 years, many of the traditional claims associated with this root have been studied scientifically. Many scientists worldwide have confirmed some of its attributes in animals (Table 1.3). In addition, there is also a rapidly increasing demand for ginseng which has warranted special efforts on the development of ginseng cultivation in China [Liu and Xiao, 1992]. This leads to substantial improvement in the quality and quantity of ginseng produced. The total national yield of ginseng in 1985 was recorded as 1560.9 tons in China (Table 1.4) [Yu, 1987].

1.2.2 Varieties of the genus Panax

Several Panax species are known to exist (Table 1.5) [Barna, 1985; Liu and Xiao, 1992] based on their place of origin. There are also other plants which are similar to the Panax species in appearance but are, in fact, botanically different despite belonging to the same family of Araliaceae. One of the well-known examples of this is Siberian ginseng or Eleutherococcus senticosus [Hou, 1977; Phillipson and Anderson, 1984; Bahrke
<table>
<thead>
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<th>Table 1.3 The Pharmacological Activities of Ginseng</th>
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<tr>
<td>Protection against radiation and liver toxicities</td>
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<tr>
<td>Modulation of cardiovascular system</td>
</tr>
<tr>
<td>Decrease platelet aggregation</td>
</tr>
<tr>
<td>Changes in blood flow</td>
</tr>
<tr>
<td>Improvement or facilitation of learning and memory processes</td>
</tr>
<tr>
<td>Anti-stress activity</td>
</tr>
<tr>
<td>Modulations of endocrine and immune systems</td>
</tr>
<tr>
<td>Modulation of cellular metabolic processes on carbohydrate, fat and protein metabolism</td>
</tr>
</tbody>
</table>

1 Yonezawa et al., 1976
2 Takeda et al., 1981
3 Yonezawa et al., 1981; 1985
4 Takeda et al., 1982
5 Zhang et al., 1987
6 Wood et al., 1964
7 Lee et al., 1981
8 Chen et al, 1984
9 Lei and Chiou, 1986
10 Matsuda et al., 1986a; 1986b
11 Kimura et al., 1988
12 Matsuda et al., 1989
13 Teng et al., 1989
14 Kaku et al., 1975
15 Hata et al., 1985
16 Liu and Xiao, 1992
17 Konno et al., 1984
18 Konno et al., 1985
Table 1.5 Varieties of *Panax* Species

<table>
<thead>
<tr>
<th>Botanical Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  <em>Panax quinquefolius</em> L.</td>
<td>North American ginseng</td>
</tr>
<tr>
<td>2  <em>Panax ginseng</em> C.A. Meyer</td>
<td>Chinese or Korean ginseng</td>
</tr>
<tr>
<td>3  <em>Panax japonicus</em> C.A. Meyer</td>
<td>Japanese ginseng</td>
</tr>
<tr>
<td>4  <em>Panax notoginseng</em> F.H. Chen</td>
<td>White ginseng</td>
</tr>
<tr>
<td>5  <em>Panax pseudoginseng</em> Wall.</td>
<td>N/A</td>
</tr>
<tr>
<td>6  <em>Panax zingiberensis</em> C.Y. Wu et K.M. Feng</td>
<td>N/A</td>
</tr>
<tr>
<td>7  <em>Panax stipuleanatus</em> H.T. Tsai et K.M. Feng</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A - not available

1 Yu, 1987
2 Barna, 1985
3 Liu and Xiao, 1992
different plants. As a result, the confusion of botanical names is an indication of the
general usage of the word, ginseng.

Although there are many varieties of ginseng, only three species are currently
considered to be medicinally active. They include *P. quinquefolius* (North American
ginseng), *P. ginseng* (Chinese or Korean ginseng), and *P. japonicus* (Japanese ginseng)
[Williams, 1957; Court, 1975; Phillipson and Anderson, 1984]. The former two varieties
have similar compositions of nutrient and certain active components (Tables 1.1; 1.2).
However, *P. japonicus* only shares two common active constituents with *P. quinquefolius*
and *P. ginseng* (Section 1.2.3.1) [Bahrke and Morgan, 1994]. Despite this difference, *P.*
*japonicus* has been used as inexpensive substitutes for the dried root of *P. ginseng*
[Bahrke and Morgan, 1994]. At present, both *P. quinquefolius* and *P. ginseng* are sold
worldwide in forms of processed roots, powders, teas and capsules [Liberti and
DerMarderosian, 1978].

1.2.3 Active Components in Ginseng

1.2.3.1 Ginseng saponins: ginsenosides

Many ginseng experts consider ginseng saponins to be the primary biologically
active components of *Panax* species [Hou, 1977; Phillipson and Anderson, 1984; Liu and
Xiao, 1992; Bahrke and Morgan, 1994]. They are known as ginsenosides (GS), of which
28 (Table 1.6) have so far been identified from the root, root-stock, stems, leaves, flowers
and flower-buds of the *P. ginseng* plant (Table 1.7) [Zhang et al., 1979; 1980; Cai et al.,
1982; Kuang and Xu., 1982; Shao and Xu, 1982; Wang et al., 1983; Wang et al., 1986;
<table>
<thead>
<tr>
<th>Part</th>
<th>Protopanaxadiol Type (%)</th>
<th>Protopanaxatriol Type (%)</th>
<th>Oleanolic Type (%)</th>
<th>Total Amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root</td>
<td>1.11</td>
<td>2.19</td>
<td>0.89</td>
<td>4.19</td>
</tr>
<tr>
<td>Root-stock</td>
<td>1.14</td>
<td>4.53</td>
<td>1.94</td>
<td>7.61</td>
</tr>
<tr>
<td>Flower-buds</td>
<td>0.95</td>
<td>5.27</td>
<td>4.69</td>
<td>10.91</td>
</tr>
<tr>
<td>Leaves</td>
<td>1.62</td>
<td>3.00</td>
<td>3.02</td>
<td>7.64</td>
</tr>
</tbody>
</table>

1 Zhang et al., 1979; 1980
2 Cai et al., 1982
3 Kuang and Xu, 1982
4 Shao and Xu, 1982
5 Wang et al., 1985
6 Xu et al., 1986a
7 Xu et al., 1986b, 1986c
dammarane series. They are named R_x, where x is either a letter, or a number, or both, according to their position on thin layer chromatogram [Phillipson and Anderson, 1984]. According to their chemical structure characteristics, they can be further divided into three types: oleanolic acid (OA), protopanaxadiol (Diol) and protopanaxatriol (Triol) (Figure 1.1) [Sprecher, 1987; Liu and Xiao, 1992].

Both *P. ginseng* and *P. quinquefolius* contain ginsenosides R_b1, R_b2, R_b3, R_c, and R_d as Diols; R_e, R_g1, and R_g2 as Triols; and R_o as OA (Table 1.1) [Sprecher, 1987]. However, they have different composition of GS. For instance, ginsenosides R_a and R_f while present in *P. ginseng* are absent in *P. quinquefolius* [Hou, 1977; Sprecher, 1987]. In addition, the approximate ratio of Diol to Triol of North American ginseng root is about 6.5 to 1. On the other hand, this ratio is close to 1 in Oriental ginseng [Hou, 1977]. Accordingly, *P. quinquefolius* contains substantially more Diol than *P. ginseng*. This can be used to explain why the Chinese believe that American root has different physiological effects from its Chinese cousin [Hou, 1977].

*P. japonicus* is one of the most famous *P. ginseng* substitutes ever used in Japan. Its GS profile is very much different from both *P. ginseng* and *P. quinquefolius*. It was reported that the Japanese root contains mainly different saponins. Only ginsenosides R_g2 and R_o are common to Japanese, Chinese or Korean and American ginsengs [Bahrke and Morgan, 1994].

There are several factors that affect the amount of GS in the *Panax* plant. GS exist not only in the root but also in other parts such as stems, root stock, leaves, flowers and flower-buds. In fact, it was illustrated that the quantities of GS varied in
Figure 1.1 Chemical structures of different ginsenosides
<table>
<thead>
<tr>
<th>Years</th>
<th>Total Ginsenosides (%)</th>
<th>R_b (%)</th>
<th>R_g (%)</th>
<th>R_a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.97</td>
<td>0.88</td>
<td>0.54</td>
<td>0.13</td>
</tr>
<tr>
<td>3</td>
<td>2.20</td>
<td>1.03</td>
<td>0.62</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>4.75</td>
<td>2.27</td>
<td>1.10</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>4.60</td>
<td>2.08</td>
<td>1.19</td>
<td>0.21</td>
</tr>
<tr>
<td>6</td>
<td>3.84</td>
<td>1.94</td>
<td>0.81</td>
<td>0.29</td>
</tr>
<tr>
<td>9</td>
<td>3.81</td>
<td>2.32</td>
<td>0.46</td>
<td>0.40</td>
</tr>
</tbody>
</table>

\(^1\) Zhang et al., 1980
growth, lowest at two years and reduce after the sixth year [Zhang et al., 1980]. This suggests that the collection period is crucial to its GS quantity which is indicative of the quality of ginseng.

1.2.3.2 Other active ginseng components: polysaccharides, polypeptides, flavonoids

Aside from GS, there are other physiologically active principles in ginseng. They include polysaccharides, polypeptides, a carboxylic acid, adenosine and flavonoids [Konno et al., 1984; Tomoda et al., 1984; Konno et al., 1985; Oshima et al., 1985; Zhu et al., 1989; Yang et al., 1990; Yang and Wang, 1991]. Ginseng glycans, a type of polysaccharides, are referred to as panaxans [Konno et al., 1984; Tomoda et al., 1984; Konno et al., 1985; Oshima et al., 1985]. The flavonoid constituents are identified as kaempferol, trifolin and panaxasenoide on the basis of chemical and spectroscopic analyses [Wang et al., 1986]. However, these compounds are only isolated from P. ginseng and have not been confirmed in other ginsengs.

1.2.4 An overview of pharmacological effects of ginseng

1.2.4.1 Ginseng as an adaptogen

Very few pharmacological and clinical studies have been conducted with North American ginseng, despite its similarity to Oriental ginseng (Tables 1.1; 1.2). In fact, the majority of scientific investigations on ginseng were done primarily with P. ginseng in the past 20 years. Since the nutrient contents and certain active components are common in
In 1970's ginseng was pharmacologically classified as an adaptogen, by Russian pharmacologists Brekhman and Dardymov [1969a]. They defined it as 'a non-specific, innocuous substance which improves the resistance of the organism to the most varied forms of stress and by its regulating actions restores, revitalizes or enhances homeostasis'.

They also concluded that the basic effect of ginseng action was its potential capacity to increase non-specific resistance to various stressors [Brekhman and Dardymov, 1969b]. Since then, *P. ginseng* had been associated with a variety of other physiological effects mostly in animals by other investigators (Table 1.3).

1.2.4.2 Ginsenosides $R_b$ and $R_g$

The majority of the pharmacological effects of ginseng listed in Table 1-3 have been attributed to GS. Among all the GS that have been identified, ginsenosides $R_b$ and $R_g$, which are Diol and Triol respectively, have attracted much of the attention. Although both *P. quinquefolius* and *P. ginseng* contain $R_b$ and $R_g$, $R_b$ and $R_g$ are the most abundant respectively in *P. quinquefolius* and *P. ginseng* (Table 1.1) [Sprecher, 1987; Chuang et al., 1995]. Early research suggested that $R_b$ suppressed central nervous system (CNS) activity and had tranquilizing properties, while $R_g$ possessed slight CNS stimulation, and vasodilator activities [Takagi et al., 1974; Owen, 1981; Bahrke and Morgan, 1994]. As $R_b$ and $R_g$ co-exist in both North American and Oriental roots, these findings seem to support the hypothesis that ginseng acts as an adaptogen which provides
1.2.4.3 **Ginseng polysaccharides and peptides**

Ginseng polysaccharides and peptides were also shown to be physiologically active. The polysaccharides were found to markedly stimulate phagocytosis of the reticuloendothelial system and the production of antibodies [Wang et al., 1980] and had hypoglycemic activity [Konno et al., 1984; Tomoda et al., 1984; Konno et al., 1985; Oshima et al., 1985; Yang et al., 1990; Yang and Wang, 1991]. It was reported that these polysaccharides increased serum complement content in guinea pig, raised serum immunoglobulin G level in mice, and elevated B-lymphatic to T-lymphatic cell ratio [Wang et al., 1980]. Consequently, ginseng polysaccharides seem to affect immune functions. Furthermore, ginseng glycans and peptides extracted from *P. ginseng* were demonstrated to have hypoglycemic activity in normal and drug-induced diabetic mice [Konno et al., 1984; Tomoda et al., 1984; Konno et al., 1985; Oshima et al., 1985; Yang et al., 1990; Yang and Wang, 1991].

1.2.4.4 **A biologically active ginseng peptide, a carboxylic acid and an adenosine**

A peptide with a molecular weight of 1400 [Ando et al., 1979; 1980], a carboxylic acid [Sekiya et al., 1981] and adenosine [Okuda and Yoshida, 1980; Sekiya et al., 1980] isolated from the water extract of *P. ginseng* were reported to be insulin-like and have anti-lipolytic properties. The carboxylic acid inhibited lipolysis induced by epinephrine and
thyrotropin [Sekiya et al., 1981]. Ginseng flavonoids were reported to influence cardiac performance and hemodynamics [Pan and Zhang., 1986].

### 1.2.4.5 Human Trials

Only a few controlled experiments in humans have been reported. Hallstrom et al. tested the effects of 1.2 g Korean ginseng or *P. ginseng* on 12 night-shift nurses, using placebo and a good night’s sleep as controls in a double-blind, crossover trial [Hallstrom et al., 1982]. Mood and body feelings were assessed before and after each treatment phase. The results indicated that there was no significant differences between placebo- and ginseng-treated phase in any of the parameters measured. However, a trend was noted, especially for mood ratings in ginseng-treated phase. As a result, the authors concluded that the duration of the study (2 weeks) and the low dosage of ginseng used might have influenced the outcome. Although blood sugar showed a decline in the experimental group, this reduction was not significant and the observed levels were in the normal range before and during the treatment.

McNaughton et al. tested Chinese and Siberian ginsengs on 30 athletes (15 males and 15 females) who were randomly assigned to either placebo, or Siberian ginseng, or Chinese ginseng group [McNaughton et al., 1989]. They were instructed to ingest 1 g of the substance at 8:00 a.m. each morning for six weeks. Results showed that Chinese ginseng- or *P. ginseng*-treated group had a significantly improved maximal oxygen uptake when compared to placebo control, while the Siberian ginseng treated group did not differ
recover as indicated by a lower post exercise heart rate, whereas Siberian ginseng had no
difference. These results suggested that Oriental ginseng seemed to be beneficial to
humans, a conclusion that remains controversial.

Engels et al. (1996) conducted a randomized, double-blind, placebo-controlled
study in which 19 healthy adult females were administered 200 mg/d of a concentrated
extract of *P. ginseng* (n = 10) or placebo (n = 9) to their otherwise supplement-free
normal diet. Before and after the trial intervention, subjects performed a graded maximal
cycle ergometry test to exhaustion and completed a standard habitual physical activity
questionnaire. Blood was analysed for lactic acid. It was found in this study that
standardized extract of *P. ginseng* had no influence on any of the variables measured and
as a result, the authors concluded that Oriental ginseng did not enhance work
performance, change energy metabolism, improve recovery response from maximal
physical work.

Recently findings by Cui et al. and Hasegawa et al. demonstrated that ginseng
saponins or GS are detectable in blood [Cui et al., 1996], urine, and feces [Hasegawa et
al., 1996] in human athletes who consumed ginseng preparations orally. These findings
indicate the uptake of ginseng saponins in humans after oral administration of ginseng
preparations.

1.2.4.5.1 Adverse effects of ginseng

The stimulant effects of ginseng and the potential problems associated with the
long term effects of the use of ginseng, primarily CNS excitation and arousal, were given the name, Ginseng Abuse Syndrome (GAS) by Siegel [1979]. GAS was defined as hypertension together with nervousness, sleeplessness, skin eruptions, edema and morning diarrhea. The range of daily dosage for individuals experiencing this syndrome was found to be 0 to 15 g. Siegel claimed that GAS was similar to organic brain syndromes associated with corticosteroids and corticotropin and might be related to ginseng’s interference with cortisone and corticotropin levels. However, Siegel’s views were based entirely upon self-reported data obtained in a survey of ginseng users as opposed to a controlled, experimental trial. In addition, Siegel clearly stated that the subjects consumed a wide variety of commercial ginseng preparations. Therefore, GAS cannot be assigned solely to ginseng in general.

1.2.5 Hypoglycemic effects of ginseng

1.2.5.1 Animal studies

1.2.5.1.1 Ginsenosides

Ginseng has been suggested to have a synergistic action with insulin and also its own hypoglycemic activity. Yokozawa et al. [1985] showed that a semi-purified saponin fraction from *P. ginseng* could stimulate various metabolic reactions involved in lipid and sugar metabolism in normal rats. Other reports indicated that most of the biochemical actions of the semi-purified saponin extract might due to ginsenoside Rb2 [Yokozawa et al., 1984]. Administration of Rb2 to streptozotocin-induced diabetic rats improved
had a significant rise of glucokinase activity in the liver and a significant decrease in glucose-6-phosphatase. This also associated with an increase in hepatic glycogen. As a result, it was concluded that R₈₂ might elicit its hypoglycemic activity by changing the levels of gluconeogenic and glycolytic enzymes and shifting the direction of the overall metabolic flow toward glucose oxidation. The results suggested that the administration of R₈₂ to diabetic rats stimulated the lipolytic activity of lipoprotein lipase, with a corresponding decrease in serum triglycerides (TG) and very low density lipoprotein (VLDL). This indicated that R₈₂ might play a role in facilitating the re-esterification of TG fatty acid and glucose in the adipose tissue [Yokozawa et al., 1985]. Consequently, the work provided some evidence that ginsenoside R₈₂ might be a useful hypoglycemic agent and that its action was very similar to the metabolic alterations produced by insulin.

1.2.5.1.2 Water (DPG-series) and methanolic (EPG-series) extracts of P. ginseng

Kimura et al. [1981a; 1982] and Waki et al. [1982] demonstrated that the water (DPG-series) and methanolic (EPG-series) extracts from P. ginseng had hypoglycemic activity in alloxan diabetic mice injected i.p. with the ginseng fraction. These extracts were first fractionated with a water-diethyl ether mixture, then the water layer was further treated with n-butanol, and the butanol layer was dialyzed. The outer dialyzates yielded the hypoglycemic extracts called DPG-3-2 and EPG-3-2. EPG-3-2 was reported to increase blood insulin secretion in normal and diabetic mice [Waki et al., 1982]. The hypoglycemic activity of EPG-3-2 in diabetic mice was abolished by an insulin antiserum,
was found to modify the metabolic clearance of insulin. Simultaneous perfusion of the pancreas with DPG-3-2 and glucose was also shown to produce an additive effect on insulin release in both normal and diabetic rats [Kimura et al., 1981b]. These findings seemed to suggest that some ginseng fractions could stimulate insulin release, especially glucose-induced insulin release from pancreatic islets, and thereby lowered blood glucose level [Waki et al., 1982]. Furthermore, although both EPG-series and DPG-series extracts had yet to be fully chemically characterized, chemical analyses on these extracts indicated that these ginseng fractions consisted of unknown substances as major components and ginseng saponins as minor components, with EPG-series containing more saponins [Kimura et al., 1981a]. However, neither one of them was more effective in lowering blood glucose than the other, suggesting that the hypoglycemic effect of ginseng fraction might not be due to the saponins present as minor components [Kimura et al., 1981a]. Therefore, the hypoglycemic component might be a new principle different from GS.

Kimura et al. [1981a] also analyzed the glucose tolerance curves of hyperglycemic KK-CA\textsuperscript{Y} mice. A comparison was been made between mice receiving a blended Chinese traditional medicine without ginseng and mice receiving the same medicine with added ginseng extract, DPG-3-2. It was observed that the mixture with DPG-3-2 decreased the rise in glucose tolerance curve, indicating that blood glucose was cleared out of circulation at a faster rate. However, the chemical structure of the active principle in DPG-3-2 had not been fully elucidated.
Aside from GS, ginseng polysaccharides were found to exhibit hypoglycemic activity. Konno et al. [1984] were the first to isolate these polysaccharides or glycans from an aqueous methanol/water extract of *P. ginseng*. There were currently ten hypoglycemic glycans recognized which were given the names panaxan A, B, C, D, E, Q, R, S, T, and U [Konno et al., 1984; Konno et al., 1985; Oshima et al., 1985]. Out of these 10 panaxans, only panaxan A was chemically characterized [Tomoda et al., 1984]. \(^1H\)-NMR spectroscopy confirmed that panaxan A was composed mainly of \(\alpha-1\rightarrow6\) linked D-glucopyranose residues having branching at the C3 position. However, \(^13\)C-NMR spectrum suggested that these \(\alpha\)-glucose units were also linked at the 1, 3, and 6 position [Tomoda et al., 1984].

All of the panaxans were demonstrated to have hypoglycemic response when injected *i.p.* into normal mice [Konno et al., 1984; Konno et al., 1984; Oshima et al., 1985]. In addition, Panaxans A, B, and U, when administered *i.p.* in alloxan-induced hyperglycemic mice, lowered plasma glucose level.

The hypoglycemic capability of ginseng polysaccharides was confirmed by Yang, 1990; Yang and Wang, 1991. This group showed that the administration of ginseng polysaccharides *i.p.* and s.c. in mice reduced blood glucose and liver glycogen. They also found an association of ginseng polysaccharides with increases in adenosine-3',5'-cyclic monophosphate (cAMP) and adenyl cyclase (AC). This action, however, was completely antagonized by propranolol, an adrenergic \(\beta\)-receptor inhibitor. In addition, both pyruvate and the activities of succinate dehydrogenase and cytochrome oxidase were found to
suggested that the action of the polysaccharides extracted from \textit{P. ginseng} was related to adrenergic receptors causing the production of cAMP which in turn activated the breakdown of glycogen for aerobic energy production. In fact, the authors believed that the polysaccharides might stimulate the release of insulin which led to a reduction in blood glucose and improvement of diabetes control.

1.2.5.1.4 \textbf{Ginseng polypeptide}

Wang et al. [1990a; 1990b] reported that ginseng polypeptide extracted from \textit{P. ginseng} possessed similar effects as ginseng polysaccharides. When ginseng polypeptide was administered \textit{i.v.} to rats, blood sugar levels and liver glycogen decreased. When mice were injected \textit{s.c.} daily for seven consecutive days, ginseng polypeptide also reduced blood glucose and liver glycogen. However, just like ginseng polysaccharides, this effect was inhibited by pretreatments of pentolamine and propranolol, suggesting that the effect of ginseng polypeptide on glucose metabolism might be related to adrenergic receptors. In addition, raised plasma glucose concentrations induced by adrenaline, glucose, or alloxan were ameliorated by ginseng polypeptide. At doses of ginseng polypeptide which caused decreases in blood glucose and liver glycogen, ginseng polypeptide also inhibited lactate dehydrogenase activity and stimulated the activities of the tricarboxylic acid cycle enzymes, succinate dehydrogenase and cytochrome oxidase. As a result, ginseng polysaccharides and polypeptides are very similar in their effects on hyperglycemia.
There have been very few well-controlled clinical studies on ginseng. However, Sotaniemi et al. [1995] recently demonstrated in a double-blind placebo-controlled study consisting of 36 non-insulin dependent diabetes mellitus patients that *P. ginseng* extract elevated mood, improved psychophysical performance, reduced fasting blood glucose (FBG), decreased body weight, and improved glycosylated hemoglobin (HbA1c), serum aminoterminalpropeptide (PIIINP), and physical activity. In addition, they reported that serum immunoreactive insulin (IRI) and lipids were not affected by ginseng therapy.

The authors suggested that the mechanism for improved FBG associated with ginseng may be multifactorial. They indicated that positive changes in psychophysical performance improved motivation for self-management, leading to changes in diet and physical activity. FBG reduction without changes in IRI suggested improved insulin sensitivity, while decreases in PIIINP by ginseng indicated reduced collagen synthesis and/or improved elimination, which might prove to be anti-antherogenic. Consequently, the authors concluded that ginseng which activated mood and psychophysical performance might improve glucose balance.

**1.2.6 Mechanism**

**1.2.6.1 Anti-stress activities of Ginseng**

A majority of early scientific research on ginseng were conducted on its stress resistant capability in the attempt to explain its adaptogenic properties. The homeostatic effect of ginseng is different from that of stimulants in that while stimulants affect
faced with a challenge or stress [Fulder, 1981]. Pharmacological studies, primarily with rodents, showed that ginseng or its active components prolonged survival to different types of stress [Brehman and Dardymov, 1969a; 1969b]. Physical stress, such as exposing animals to very hot or cold environments, lethal X-rays, excessive physical work; chemical stress, such as subjecting animals to medications, poisons, narcotics, toxic anti-cancer drugs; and biological stress, such as bacterial infections, malaria, surgery, implantation of cancer, and artificially induced diabetes have all been used for more than twenty years to study the capability and the mechanism of ginseng in eliciting its adaptogenic properties, and to evaluate its efficacy as claimed by TCM [Fulder, 1993].

It has generally been agreed that the ability of ginseng to restore homeostasis when the organism is subject to stress is closely related to the control of the stress hormones. It is known that corticosteroids and adrenocorticotropin hormone (ACTH) bind directly to brain tissue in order to increase mental activity during stress and challenge. Fulder [1981] showed that in rats which had been both adrenalectomized and ovariectomized, administration of ginseng saponin mixture i.p. for seven days caused a substantial increase in binding of corticosteroid in lower brain regions two hours after the injection of tritiated corticosterone. The purpose of removing the adrenal glands and ovaries from the rats was to retard the internal production of corticosterone. However, when radio-labeled dexamethasone, a glucocortical analogue, was used instead of corticosteroid, no differences were observed between ginseng-treated and control rats. This suggested that ginseng bound specifically on corticosterone. Although the increase in binding of
injection due to reduced corticosteroid degradation in the liver, an analysis of cytochrome P450 activity in the liver did not support this possibility. In addition, an experiment on the content of receptor molecules in neurons of the hippocampus showed that there were similar quantities of receptor in ginseng- and saline-treated rats. As a consequence, Fulder suggested that there might be an interference with the feedback control of steroid levels in the body which was established by the hypothalamus, through the pituitary.

Indeed, other investigators also found that GS acted on the pituitary-adrenocortical system. Using radioimmunoassay and competitive protein binding method, Hiai et al. [1979] demonstrated the injection of ginseng saponin mixture i.p. increases plasma ACTH and corticosterone at 30, 60, and 90 minutes after the treatment. Isolated GS, Diol or Triol, also elevated plasma corticosterone. However, the ginseng-induced increase in plasma corticosterone was suppressed by pretreatment with dexamethasone. Hiai et al. [1979] concluded that ginseng saponin acted on the hypothalamus and/or hypophysis primarily, and stimulated ACTH secretion which resulted in increased synthesis of corticosterone in the adrenal cortex.

Fulder [1981] proposed that the adaptogenic or harmonizing nature of ginseng involved stress steroids. After the ingestion of ginseng, the hypothalamus became more sensitive to stress hormones. When stress occurs, the sensitized hypothalamus acted on the pituitary to produce large amounts of ACTH which, in turn, acted on the adrenal glands to manufacture more stress steroids. If stress is prolonged, the sensitized hypothalamus would detect the level of stress steroids in the body and shut down the
stress hormones during stress and shut down more quickly when stress stopped. Fulder [1981] further indicated that the active principles for the regulation of internal harmony were GS which were quite similar to steroids in chemical structure (Figure 1.1).

1.2.6.2 Diabetes Mellitus

Non-insulin diabetes mellitus (NIDDM) affects between 5 and 20% of the population in Western industrialized societies [Harris, 1989] and is associated with a significant amount of morbidity and mortality [Assmann and Schulte, 1988]. However, there still exist many uncertainties with regards to the pathogenesis of the disease despite decades of investigative efforts. It has recently been suggested that NIDDM may be more related to the abnormalities in fat than carbohydrate metabolism [McGarry, 1992].

Approximately 85% of NIDDM patients in the United States are obese [Lillioja et al., 1988; Eriksson et al., 1989] and that obesity is associated with increased lipolysis, reflected by increased systemic glycerol and FFA concentrations [Gorden, 1960; Reaven et al., 1960]. In addition, obesity is also associated with insulin resistance, which has been suggested to be the earliest detectable metabolic defect in patients with NIDDM [Lillioja et al., 1988; Eriksson et al., 1989]. It was shown in both animals and humans that weight gain decreased insulin sensitivity and glucose tolerance, while weight loss increased them [Goto et al., 1954; Schliack, 1954; Sims et al., 1973; Pascoe and Storlien, 1990]. It remains unclear, however, how obesity causes insulin insensitivity. Nevertheless, it was shown that elevated plasma FFA inhibited insulin-stimulated glucose uptake in healthy
In insulin-dependent diabetes mellitus (IDDM), excess lipolysis is often associated with hypoinsulinemia. However, adequate insulin therapy usually normalizes plasma FFA and triglycerides (TG) levels [Arner et al., 1980]. As a consequence, NIDDM differs in that it is linked to excess lipolysis and hepatic reesterification of FFA to TG which contributes to high density lipoprotein (HDL) lowering [Kissebah, 1976; Kissebah et al., 1982; Yki-Jarvinen et al., 1989]. Although therapeutic intervention may improve glycemic control in NIDDM, lipoproteins abnormalities usually persist and thereby, increases the risk of atherosclerosis [Hollenbeck et al., 1986].

### 1.2.6.3 Possible Mechanism of Ginseng in Lowering Postprandial Glycemia

Glucocorticoids are hormones that also play a role in the regulation of carbohydrate metabolism in addition to insulin. Although the complex actions of these steroids secreted from the adrenal cortex are not completely understood, their effects on carbohydrate metabolism are to facilitate glucagon in its gluconeogenetic action during fasting. They also inhibit glucose uptake into various peripheral tissues [Moffett et al., 1993].

Glucocorticoid concentrations vary throughout the day [Dinneen et al., 1993]. In fact, plasma level of cortisol increases substantially during sleep. As a consequence, plasma cortisol in the morning has been found to be acutely elevated [Dinneen et al., 1995]. High levels of glucocorticoids or counter-regulatory hormones in plasma lead to
When an animal or human is exposed to stress, such as homeostatic stress in the case of fasting, secretion of ACTH is elevated which brings about a corresponding increase in glucocorticoids [Moffett et al., 1993]. Therefore, elevated levels of glucocorticoids are also associated with stress to the body. During an overnight fast, the body has continuously been exposed to homeostatic stress which results in an elevation of glucocorticoids. The administration of North American ginseng sensitizes the hypothalamus by its GS content which, in turn, detects the high level of glucocorticoids and shuts down their production quickly [Fulder, 1993]. With the rapid decline of glucocorticoids, insulin sensitivity improves. Consequently, when a meal is ingested, the body is prepared or stimulated to clear the postprandial rise in blood glucose out of the circulation more efficiently. This is not only useful in normal humans, it may also be helpful to NIDDM patients in their daily blood glucose and lipid management.

1.2.7 Conclusion to Literature Review

Ginseng has been used for several thousand of years in China as a tonic, prophylactic agent and 'restorative'. However, its traditional claims on enhancing overall body health have been established primarily through clinical or anecdotal experience as opposed to scientific verification of its pharmacological effects. In the past 20 years, much scientific research has been conducted on animals to evaluate the efficacy of ginseng, while there have been very few well-controlled studies on humans. In addition,
Chemical analyses show that *P. ginseng* and *P. quinquefolius* have many GS in common which are considered to be the active ginseng components responsible for many pharmacological effects, including improvement of hyperglycemia in diabetic rats. The hypoglycemic effect of ginseng has been repeatedly demonstrated in animals. In humans, however, there have been few studies until the recent publication by Sotaniemi et al. (1995) who showed with NIDDM patients that ginseng extract could elevate mood, improved psychophysical performance, reduced FBG, decreased body weight and improved HbA1c, serum PIIINP, and physical activity. This is perhaps the first demonstration of ginseng efficacy in NIDDM management in humans.

As a consequence, recent findings suggest that Oriental ginseng may be beneficial in controlling NIDDM. It, however, remains unclear whether North American ginseng possesses similar physiological effects in humans as the Oriental root despite the similarity of their chemical and nutrient profiles (Tables 1.1, 1.2). Furthermore, it is also uncertain what the optimal dose and time of administration are for either ginseng type. Therefore, there exists a need to investigate whether whole North American ginseng root or *P. quinquefolius* have any effects on postprandial blood glucose in normal humans and to determine what the most optimal time and dose of administration are before conducting studies on NIDDM with North American ginseng root.

### 1.3 Research Hypothesis and Objectives

The hypothesis is that North American ginseng or *P. quinquefolius* lowers
The main objectives are:

1. To determine whether *P. quinquefolius* causes a lower postprandial blood glucose response when taken together with a glucose challenge.

2. To determine if North American ginseng lowers postprandial glycemic response when taken before a glucose challenge.

3. To determine the most optimal time and dose of administration of North American ginseng in lowering postprandial glycemia.
CHAPTER TWO

EFFECTS OF NORTH AMERICAN GINSENG ON POSTPRANDIAL GLYCEMIA
- TAKEN TOGETHER WITH A GLUCOSE CHALLENGE -
2.1 Introduction

The traditional method of consuming ginseng is to either to ingest the root or boil the root in four volumes water until the level becomes one volume. It is normally taken on an empty stomach [Personal communication, Li., 1996]. The usual daily dose of Oriental ginseng in Korea is 6.4 g per day [Personal communication, Park, 1996]. It has been advised that since North Americans have generally large body size, a higher dose may be required [Personal communication, Park, 1996]. Furthermore, in TCM, the daily dose of non-toxic herbs is usually in the range of 3 to 10 g, given as decoction or in pill or powder form [Bensky and Gamble 1983].

2.2 Aim

The main objective of this study was to determine whether North American ginseng or P. quinquefolius can lower postprandial blood glucose when taken together with a glucose challenge. Doses of 3 g, 6 g, and 9 g North American ginseng powder were selected for this study in light of the Bensky and Gamble publication [1983].
2.3.1 Glucose challenge preparation and composition

The oral glucose drink (250 mL) was made by diluting 100 mL standardized glucose solution (75 g glucose / 300 mL) (Glucodex, Rougier Inc.) with 150 mL of water. It consisted of 25 g available CHO. It was prepared fresh on each study day.

2.3.2 Powder form of North American ginseng

The nutrient profile of the North American ginseng powder used in this study is shown on Table 1.2. The powder was made by grinding the root hair taken from four to five years old *P. quinquefolius* grown in Ontario or British Columbia, Canada (Atkins Farm Ltd., Ontario; Chai-Na-Ta Corp., B.C.). The powder was encapsulated in gelatin capsules, with each capsule containing either 490 mg or 500 mg of North American ginseng powder. All the ginseng powder capsules used in the study were generously supplied by the two manufacturers (Atkins Farm Ltd., Ontario; Chai-Na-Ta Corp., B.C.) and were obtained from the same manufacturers’ batch.

2.3.3 Subject recruitment and profile

Healthy non-smokers, with no previous history of diabetes or related metabolic diseases, were recruited to participate in the study. None of them were not taking any medications. Written consent (Appendix I), approved by the Human Subjects Review Committee at University of Toronto, was obtained from each subject after they had been fully informed about the procedure and involvement required in the study.
28.6 ± 3.1 years. The mean BMI was 24.0 ± 1.1 kg/m² and the mean fasting blood glucose (FBG) was 4.7 ± 0.1 mmol/L. Subject characteristics are listed in Table 2.1.

2.3.4 Experimental Design

This study made use of a randomized, cross-over design in which each subject is his/her own control. The oral glucose drink was prepared on each test day for the subjects. Subjects were evaluated on six occasions. The control (glucose challenge) was administered three times. The treatments consisted of three different doses of *P. quinquefolius* powder taken together with the glucose drink as treatment, after a 10 to 12 hour-overnight fast. Each of the subjects was randomized in an unique sequence of test order as follows:

C — Tₓ — C — Tᵧ — Tz — C

(C = control, T = North American ginseng tests, x,y,z = different doses) The control was administered three times in order to standardize intra-individual variation. In addition, there was a washout period of at least two days between each test. Subjects were asked to repeat a specific test if the result was significantly different (± 2 SD) from the group mean.
Subjects were asked to come to the Risk Factor Modification Centre at St. Michael's Hospital after a 10 to 12 hour-overnight fast. Finger-prick capillary blood samples (250 μL) were taken at fasting and 15, 30, 45, 60, 90, and 120 minutes after consumption of control or test. Before, collecting fasting blood, subjects were required to be seated for 10 minutes and remain seated for the duration of the study. After the fasting sample had been obtained, subjects were instructed to consume the glucose challenge either with various doses of ginseng powder (3 g, 6 g, or 9 g) (T) or without ginseng for control (C) steadily in 10 minutes. Finger-prick capillary blood samples were obtained with Autolet Lancets (Owen Mumford Ltd., Woodstock, Oxon). Blood samples were contained in pre-labeled fluoro-oxalate tubes and were kept frozen at -20°C prior to glucose analysis within 48 hours.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=8)</th>
<th>Males (n=5)</th>
<th>Females (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(range)</td>
<td>(range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.6 ± 3.1</td>
<td>30.4 ± 5.0</td>
<td>25.7 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>(22.0 to 49.0)</td>
<td>(23.0 to 49.0)</td>
<td>(24.0 to 29.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 1.1</td>
<td>24.9 ± 1.4</td>
<td>22.4 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>(20.3 to 28.4)</td>
<td>(20.6 to 28.4)</td>
<td>(20.3 to 25.6)</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(4.4 to 5.0)</td>
<td>(4.4 to 5.0)</td>
<td>(4.6 to 4.8)</td>
</tr>
</tbody>
</table>
Capillary blood glucose concentrations were measured using an automatic analyzer (2300 Stat Glucose Analyser, Yellow Springs Instruments, Yellow Spring, OH). This device utilizes the glucose oxidase technique [Shimizu et al., 1980]. A standard glucose solution, prepared by dissolving 1.8 g D-glucose in 1.0 L of distilled water, was used to calibrate the glucose analyser. All the samples were analysed only after two successive readings of the standard solution between 9.9 to 10.1 mmol/L had been attained.

The glucose analyser is dependent on glucose oxidase to measure glucose concentrations in blood. When $\alpha$-D-glucose in blood samples makes contact with the immobilized enzyme, glucose oxidase, it is rapidly oxidized producing hydrogen peroxide ($H_2O_2$). This $H_2O_2$ is, in turn, oxidized at the platinum anode, producing electrons. A dynamic equilibrium is achieved when the rate of $H_2O_2$ production and the rate at which hydrogen peroxide leaves the immobilized glucose oxidase layer are equivalent. This equilibrium is indicated by a steady state response. The electron flow is linearly correlated to the steady state of $H_2O_2$ concentration and therefore, also to the concentration of glucose.

2.3.7 Statistical analysis

Results were expressed as mean ± standard error (SE). Incremental area under the glucose curve (AUC), omitting area beneath the fasting level, was calculated geometrically [Wolever et al., 1991]. Statistical comparisons of data at specific time points, glucose peak, and AUC were done by repeated measures ANOVA. Newman-Keuls method was
2.4 Results

2.4.1 Effects of North American ginseng on postprandial glycemic response when taken together with a glucose challenge

There was no statistically significant difference at any of the time points, glucose peak, nor AUC (Figures 2.1; 2.2; Table 2.2) among the control, and 3 g, 6 g, and 9 g ginseng treatment. The mean ± SE of all the time points and AUC are listed on Table 2.2.
Figure 2.1 Effect of North American ginseng taken together with a glucose challenge on postprandial glycemic response (n = 8). Values are means ± SE.
Figure 2.2 Incremental area under glycemic response curve: North American ginseng taken together with a glucose challenge (n = 8). Values are means ± SE.
Table 2.2  Blood glucose concentrations at specific time points, change in blood glucose peak and incremental areas under the curve (AUC).

<table>
<thead>
<tr>
<th>Ginseng (g)</th>
<th>Blood glucose concentrations (mmol/L)</th>
<th>AUC (mmol.min/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0'</td>
<td>15'</td>
</tr>
<tr>
<td>Control</td>
<td>4.6 ± 0.1</td>
<td>6.5 ± 0.3</td>
</tr>
<tr>
<td>3</td>
<td>4.7 ± 0.3</td>
<td>7.1 ± 0.3</td>
</tr>
<tr>
<td>6</td>
<td>4.6 ± 0.1</td>
<td>7.1 ± 0.2</td>
</tr>
<tr>
<td>9</td>
<td>4.8 ± 0.1</td>
<td>6.1 ± 0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SE
The results indicated that there were no statistically significant differences in postprandial blood glucose response between the treatments (3 g, 6 g and 9 g of North American ginseng taken with a glucose challenge) and the control (the glucose challenge without any ginseng treatment).

However, one possible explanation might be that since ginseng did not interact with the food, there was no change in the physical nature of food, such as changing food viscosity as seen in the case of some soluble dietary fibres. The administration of ginseng together with the glucose drink did not therefore, cause any changes in glucose absorption rate. If ginseng caused any reduction in postprandial glycemia, it might be a result of some other biological pathway. In other words, it might be certain pharmacological phenomena rather than the physical alteration of food which entraps nutrients.
CHAPTER THREE

EFFECTS OF NORTH AMERICAN GINSENG ON
POSTPRANDIAL GLYCEMIA
- TAKEN PRIOR TO A GLUCOSE CHALLENGE -
3.1 Introduction

In the previous experiment (Chapter 2), it was shown that when ginseng was taken together with a glucose drink, it did not reduce postprandial blood glucose. Therefore, it was hypothesized that ginseng might elicit its blood glucose lowering effects through systemic pharmacological pathway other than physical nature of nutrients. The traditional way of consuming ginseng is on empty stomach [Personal communication, Li, 1996]. Perhaps, ginseng should be taken before the glucose challenge so that it can ‘prime’ or ‘prepare’ the system for physiological challenges.

3.2 Aim

The objective of this experiment was, therefore, to determine if North American ginseng can reduce postprandial glycemia when it is administered before the glucose challenge. The same oral glucose drink as Experiment 1 (Chapter 2) and 9 g of *P. quinquefolius* were used in this experiment. Finger-prick capillary blood samples were collected at various time points and glucose concentrations were measured.
3.3 Materials and Methods

3.3.1 The compositions of glucose challenge and North American ginseng
Both the glucose drink and the ginseng powder used in this experiment were the same as the ones used in the previous experiment (Sections 2.3.1; 2.3.2).

3.3.2 Subject recruitment and profile
The subject selection criteria were the same as Experiment 1 (Chapter 2). Written consent (Appendix I), approved by the Humans Subject Review Committee, University of Toronto, was submitted by each subject.

Seven subjects (3 males + 4 females) were recruited. They were all normal at the time of the study. Their mean age, BMI, and FBG were 31 ± 4.2 years, 23 ± 1.2 kg/m², and 4.5 ± 0.1 mmol/L respectively. Subject characteristics are shown in Table 3.1.

3.3.3 Experimental design
This experiment employed a randomized, cross-over design. Thus, each subject acted as his/her own control. There were a total of three separate tests, consisting of a glucose challenge, ginseng control, and ginseng treatment (Figure 3.1). Subjects were randomized to various sequences of test order. They were asked to perform each test after a 10 to 12 hour-overnight fast. The glucose drink was prepared fresh on each test day.
Figure 3.1 Experimental design

**Glucose Control**  
300 mL water  
250 mL glucose drink

**Ginseng + Glucose**  
300 mL water  
250 mL glucose drink  
+ 9 g ginseng

**Ginseng Control**  
300 mL water  
250 mL water  
+ 9 g ginseng
3.3.4 Study procedure and blood sample collection

Subjects were requested to attend the Risk Factor Modification Centre at St. Michael's Hospital following a 10 to 12 hour-overnight fast. Upon arrival, subjects were asked to remain seated throughout the duration of the study. Fasting finger-prick capillary blood sample was taken at the beginning using Autolet Lancets (Owen Mumford Ltd., Woodstock, Oxon), followed by an ingestion of 9 g North American ginseng powder contained in gelatin capsules with 250 to 400 mL of water. After 80 minutes, another finger-prick blood sample was obtained. A glucose challenge, consisted of 25 g glucose, was then consumed. Further finger-prick blood samples were collected at 15, 30, 45, 60, and 90 minutes after the glucose challenge.

For glucose and ginseng controls, finger-prick blood samples were also collected at the same specified time points. For the glucose control, 300 mL of water was given without any ginseng prior to the glucose challenge. For the ginseng control, 250 mL of water was ingested instead of the glucose drink following the consumption of 9 g ginseng powder. This protocol provided possible control for postprandial glycemic response attributed to North American ginseng powder.

All blood samples were collected in pre-labeled fluoro-oxalate tubes. They were kept frozen at -20 °C before glucose analysis within 48 hours.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=7)</th>
<th>Males (n=3)</th>
<th>Females (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE (range)</td>
<td>Mean ± SE (range)</td>
<td>Mean ± SE (range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.0 ± 4.2 (23.0 to 49.0)</td>
<td>33.7 ± 7.9 (23.0 to 49.0)</td>
<td>29.0 ± 5.3 (23.0 to 45.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 1.1 (20.1 to 28.4)</td>
<td>25.1 ± 1.7 (23.4 to 28.4)</td>
<td>23.1 ± 1.7 (20.3 to 28.0)</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>4.5 ± 0.1 (4.3 to 4.9)</td>
<td>4.6 ± 0.1 (4.3 to 4.9)</td>
<td>4.5 ± 0.1 (4.2 to 4.8)</td>
</tr>
</tbody>
</table>
3.3.5 Blood glucose analysis

Capillary blood samples were measured using the same procedure and equipment as the previous experiment (Section 2.3.6).

3.3.6 Statistical analysis

Results were expressed as mean ± SE. Statistical comparisons of data at specific time points, glucose peak, and AUC were done by one-way ANOVA with repeated measures. Newman-Keuls method was used as a post test to compare individual means for multiple comparisons. Differences were considered to be statistically significantly different if p < 0.05.

3.4 Results

3.4.1 Effects of North American ginseng on postprandial blood glucose response when taken before the glucose challenge

Ginseng + glucose resulted in a 30.3 ± 6.4% decrease (p < 0.01) in AUC from that of the glucose alone (Figure 3.1). Both the AUC of the glucose alone and ginseng + glucose were substantially larger (p < 0.001) than that of the ginseng alone (Table 3.2). In fact, the AUC of ginseng alone was determined at 1.6 ± 1.4 mmol.min/L, while the AUC of the glucose alone and ginseng + glucose were respectively found to be 120.0 ± 9.4 and 82.3 ± 8.2 mmol.min/L (Figure 3.1).

North American ginseng taken at 80 minutes prior to the glucose load produced a significantly lower (p < 0.05) blood glucose concentration on the postprandial glycemic
Blood glucose concentrations at 15, 30, 45 and 60 minutes on the ginseng control curve were also significantly lower ($p < 0.05$) than that on both the glucose control and ginseng treatment (Table 3.2).
Figure 3.2 Incremental area under glycemic response curve:
North American ginseng taken prior to a glucose challenge (n = 7).
Values are means ± SE. Means with different letters differ significantly (p < 0.05) by ANOVA.
Table 3.2  Blood glucose concentrations at specific time points, change in blood glucose peak, and incremental areas under the curve (AUC)

<table>
<thead>
<tr>
<th>Blood glucose concentrations (mmol/L)</th>
<th>AUC (mmol.min/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-80' 0' 15' 30' 45' 60' 90' A in Glucose Peak</td>
</tr>
<tr>
<td><strong>Ginseng alone</strong></td>
<td>4.5 ± 0.1 4.5 ± 0.1 4.4 ± 0.1 4.4 ± 0.2 4.3 ± 0.1 4.4 ± 0.1 0.2 ± 0.1</td>
</tr>
<tr>
<td><strong>Glucose alone</strong></td>
<td>4.5 ± 0.1 4.5 ± 0.1 5.9 ± 0.3 7.7 ± 0.3 6.9 ± 0.2 5.0 ± 0.3 4.2 ± 0.1 3.3 ± 0.2</td>
</tr>
<tr>
<td><strong>Ginseng + Glucose</strong></td>
<td>4.5 ± 0.1 4.6 ± 0.1 6.2 ± 0.1 7.1 ± 0.2 5.8 ± 0.4 4.8 ± 0.3 4.2 ± 0.1 2.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SE. Means with different letter superscripts within a column differ significantly (p<0.05) as determined by ANOVA followed by Neuman-Keuls method.
Figure 3.3 Effect of North American ginseng on postprandial blood glucose when taken prior to a glucose challenge (n = 7). Values are means ± SE. Means with different letters vertically differ significantly (p < 0.05) by ANOVA.
3.5 Discussion

The results indicated that 9 g *P. quinquefolius* powder when administered 80 minutes prior to glucose challenge reduced postprandial blood glucose peak at 30 minutes and decreased AUC by 31.4%. AUC on the ginseng control curve was found to be negligible which indicated that ginseng powder alone did not contribute significantly to the postprandial rise in blood glucose. As a result, AUC on the ginseng treatment curve did not need to be adjusted.

This finding showed that North American ginseng taken prior to glucose load was effective in lowering post-meal blood glucose in normal humans, which might indicate that it was a pharmacological effect. However, it remained uncertain whether there was an effective time and dose of administering ginseng powder.
CHAPTER FOUR

OPTIMAL TIME AND DOSE OF
NORTH AMERICAN GINSENG ADMINISTRATION
4.1 Introduction

*P. quinquefolius* has been demonstrated to lower postprandial blood glucose response when taken prior to a glucose load (Chapter 3). This finding is the first time in which North American ginseng is shown to have a postprandial hypoglycemic response in healthy humans. This effect, however, is not seen when administered together with the glucose drink (Chapter 2). Thus, the purpose of this phase is to determine the optimal time and dose of taking North American ginseng powder.

4.2 Aim

The main purpose of this study was to find the optimal dose and time of taking North American ginseng powder such that the maximal postprandial hypoglycemic effect can be elicited. Doses of 3 g, 6 g, and 9 g of *P. quinquefolius* were selected as Experiment 1 for the same reason (Chapter 2). Each of these doses will be taken at 40, 80, and 120 minutes before the glucose challenge.

4.3 Materials and Methods

4.3.1 The composition of standard meal and North American ginseng

Both the standard meal and the ginseng powder used in this study was the same as the ones used in the previous experiments (Sections 2.3.1; 2.3.2).
The requirements for selecting subjects for this phase were identical to the ones in Experiments 1 and 2 (Chapters 2; 3). All subjects were asked to return a signed consent form (Appendix 1) that had been approved by the Humans Subject Review Committee of University of Toronto.

There were altogether six subjects (4 males + 2 females) participated in this study. They were all healthy non-smokers at the time of the study. They had an average age of 36.7 ± 5.4 years, a mean BMI of 25.1 ± 1.3 kg/m^2, and a mean FBG of 4.4 ± 0.1 mmol/L. Subject characteristics are shown in Table 4.1.

4.3.3 Experimental design

This study employed a randomized, cross-over design in which each subject is his or her own control. There were a total of twelve tests, comprising three different doses of North American ginseng (3 g, 6 g, and 9 g), each of which was taken at three different times (-120, -80, and -40) prior to meal, and three glucose controls. There was a washout period of at least two days. All subjects were randomized to an unique sequence of test order as follows:

\[ C - T_1 - T_2 - T_3 - T_4 - T_5 - C - T_6 - T_7 - T_8 - T_9 - C \]

where C = control, T = North American ginseng test, and 1,...,9 = different dose and time

They were also asked to perform each test after a 10 to 12 hour overnight fast. The oral glucose drink was prepared on each test day.
4.3.4 Study procedure and blood sample collection

Subjects were asked to come to the Risk Factor Modification Centre, St. Michael’s Hospital following a 10 to 12 hour overnight fast. Throughout the duration of the study, all participants were asked to remain seated. A fasting blood sample was collected before any ingestion using Autolet Lancets (Owen Mumford Ltd., Woodstock, Oxon). For the control (C), subjects were asked to consume a glucose drink, which consisted of 25 g glucose, and collect blood at 15, 30, 45, 60, and 90 minutes. For ginseng powder tests (T), either 3 g, 6 g, or 9 g North American ginseng powder was taken with 300 mL water. After either 40, 80, or 120 minutes, another finger-prick blood sample was obtained. A glucose drink, containing 25 g glucose, was then consumed. Further capillary blood samples were collected at 15, 30, 45, 60, and 90 minutes after ingestion of the glucose challenge. All blood samples were contained in pre-labeled fluoro-oxalate tubes. They were kept frozen at -20 °C before glucose analysis within 48 hours.

4.3.5 Blood glucose analysis

Finger-prick capillary blood samples were measured using the same procedure and equipment described in Chapter 2 (Section 2.2.6).
4.3.6 Statistical Analysis

Results were presented as mean ± SE. Statistical comparisons of AUC for all three doses and time of ginseng administration were done by two-way ANOVA (Table 4.2). One-way ANOVA with repeated measures was employed to further compare the effectiveness of each given dose ingested at each specified time with that of the control. Comparisons of data at specific time points for each dose with glucose control were done by one-way ANOVA. Newman-Keuls post test was used to compare individual means for multiple comparisons following both two-way ANOVA and one-way ANOVA. Differences were statistically significant if p < 0.05.

4.4 Results

When 3 g and 6 g of North American ginseng powder were taken at either 40 (p < 0.05) or 80 minutes (p < 0.05) prior to the glucose drink, it resulted in a lower AUC as compared to glucose alone. Lower AUC’s were also seen when 9 g of P. quinquefolius powder was ingested at either 40 (p < 0.01), 80 minutes (p < 0.01), or 120 minutes (p < 0.05) before the glucose challenge. (Figure 4.1). However, AUC’s for all three doses of ginseng powder taken at 40, 80, and 120 minutes before glucose challenge were not significantly different (Table 4.2). In addition, neither time, dose nor the interaction between time and dose appeared to contribute to the overall reduction of postprandial glycemia.
ginseng powder at either 40, 80, or 120 minutes before the glucose load are shown in Figure 4.2. Although there was no significant difference, it appeared that 3 g, 6 g, and 9 g of ginseng powder ingested 40 minutes prior to glucose load tended to have greater reductions in postprandial hypoglycemic response (Figure 4.2).

Lower blood glucose concentrations at 45 minutes were found when 3 g, 6 g, 9 g ginseng were taken at 40 and 80 minutes before glucose challenge when compared to glucose alone (Figures 4.3; 4.4; 4.5).
Table 4.1 Subject Profile.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=6)</th>
<th>Males (n=4)</th>
<th>Females (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE (range)</td>
<td>Mean ± SE (range)</td>
<td>Profile</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.7 ± 5.4 (23.0 to 49.0)</td>
<td>36.8 ± 7.1 (23.0 to 49.0)</td>
<td>25.0 and 48.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 1.3 (20.2 to 28.9)</td>
<td>25.3 ± 1.1 (23.6 to 28.4)</td>
<td>20.2 and 28.9</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>4.4 ± 0.1 (4.4 to 4.9)</td>
<td>4.4 ± 0.1 (4.4 to 4.9)</td>
<td>4.2 and 4.8</td>
</tr>
</tbody>
</table>
Figure 4.1 Incremental area under glycemic response curve: 3 g, 6 g, 9 g of North American ginseng powder taken at -40, -80, -120 minutes before a glucose challenge (n=6). Values are means ± SE. Means with different letters differ significantly (p < 0.05) by ANOVA.
American ginseng powder administration time, dose, and time-dose interaction.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1073.2</td>
<td>2</td>
<td>536.6</td>
<td>0.58</td>
<td>0.5613</td>
</tr>
<tr>
<td>Time</td>
<td>2445.5</td>
<td>2</td>
<td>1222.7</td>
<td>1.33</td>
<td>0.2739</td>
</tr>
<tr>
<td>Dose-Time Interaction</td>
<td>182.9</td>
<td>4</td>
<td>45.7</td>
<td>0.05</td>
<td>0.9952</td>
</tr>
</tbody>
</table>
Figure 4.2 Percent reduction in AUC with different time and dose of North American ginseng powder administration (n=6). Values are means ± SE.
Figure 4.3  Effects of 3 g North American ginseng on postprandial blood glucose when taken at 40, 80, 120 minutes prior to a glucose challenge (n = 6). Values are means ± SE. Means with different letters vertically differ significantly (p < 0.05).
Figure 4.4 Effects of 6 g North American ginseng on postprandial blood glucose when taken at 40, 80, 120 minutes prior to a glucose challenge (n = 6). Values are means ± SE. Means with different letters vertically differ significantly (p < 0.05).
Figure 4.5 Effects of 9 g North American ginseng on postprandial blood glucose when taken at 40, 80, 120 minutes prior to a glucose challenge (n = 6). Values are means ± SE. Means with different letters vertically differ significantly (p < 0.05).
These results confirmed the previous finding (Chapter 3) that 9 g of North American ginseng powder administered 80 minutes before a glucose challenge resulted in a decreased postprandial blood glucose response ($p < 0.01$) as shown by a lower AUC compared to glucose alone (Figure 4.1).

North American ginseng powder (3 g, 6 g, 9 g) taken either at 40 or 80 minutes before glucose challenge lowered postprandial glycemic response by decreasing blood glucose concentrations at 45 minutes after the glucose load (Figures 4.3; 4.4; 4.5). Neither time nor the interaction between time and dose appeared to play a role in reducing postprandial glycemic response (Table 4.2). However, a trend was be seen (Figure 4.1) in that North American ginseng powder (3 g, 6 g, 9 g) taken closer to the glucose challenge time appeared to cause a greater decrease in AUC. This level of reduction seemed to gradually diminish as ginseng was ingested further from glucose ingestion time. A greater sample size would be necessary to confirm this trend.

Since there was no significant difference in percent reduction of AUC among the three dosages taken at three difference times, an optimal time and dose of administering North American ginseng powder could not be determined. This might suggest that lower doses of ginseng need to be further tested. However, it could be concluded that lower doses of ginseng powder (3 g and 6 g) elicited postprandial hypoglycemic responses in normal healthy humans when they were taken shortly before the glucose challenge (40 and 80 minutes). A high dose of North American ginseng powder (9 g) produced lower
gyr. The responses after glucose ingestion when it was taken either at a short or long period of time prior to the glucose challenge (40, 80, 120 minutes) (Figure 4.1).
CHAPTER FIVE

GENERAL DISCUSSION

AND

CONCLUSION
5. GENERAL DISCUSSION AND CONCLUSION

5.1 General discussion and future research

Previous studies with animals and humans have suggested that Oriental ginseng may be useful in treating diabetes [Kimura et al., 1981a; 1981b; Kimura and Suzuki, 1982; Waki et al., 1982; Konno et al., 1984; Yokozawa et al., 1984; Konno et al., 1985; Oshima et al., 1985; Wang et al., 1985; Yokozawa et al., 1985; Sotaniemi et al., 1995]. These findings seem to support the traditional claim that Oriental ginseng is an effective treatment for diabetes (Section 1.2.1.5). Chemical analyses of Oriental and North American ginseng have shown that they both contain many reputedly active components and have very similar nutrient profiles (Tables 1.1; 1.2). Consequently, it was hypothesized in this study that North American ginseng also possesses similar hypoglycemic effects as its Asian cousin.

Recent findings by Cui et al. [1996] and Hasegawa et al. [1996] demonstrated that ginseng components could be absorbed. This group was able to detect GS fragments in blood, urine, and feces in human athletes who consumed ginseng preparation orally, suggesting that ginseng saponin fragments were absorbed after oral ingestion. In addition, animal studies in which ginseng components and fractions extracted from Oriental ginseng root were injected i.p. into both chemically-induced and genetic diabetic rats, as well as normal rats had shown to have hypoglycemic properties [Konno et al., 1984; Konno et al., 1985; Oshima et al., 1985]. Since i.p. injection in animals can be extrapolated to oral
that oral administration of ginseng may have blood glucose lowering effects in humans.

The present study demonstrated that oral ingestion of North American ginseng with a glucose challenge does not cause any reduction in postprandial blood glucose response (Chapter 2), while consumption of *P. quinquefolius* prior to the glucose challenge has considerable postprandial hypoglycemic response (Chapters 3; 4). It appears that since ginseng does not alter the physical nature of food, for example the viscosity of certain soluble fibres, no change in postprandial blood glucose results when ginseng is taken together with the glucose load. This suggests that the reduction in blood glucose response after the glucose drink may due to a pharmacological effect rather than a physical modification of food causing a decrease in absorption rate in the small intestine. However, there remain uncertainties about the optimal dose, and whether the time of ingestion prior to the glucose challenge is a contributing factor to reducing postprandial glycemia. Nevertheless, this study is the first to demonstrate that North American ginseng powder when taken orally produces a lower postprandial glycemic response in healthy individuals. In addition, it also seems to suggest that the effective dose of North American ginseng powder may be lower than 3 g.

Although decreases in blood glucose and insulin rise after ingestion of carbohydrate-rich meals sometimes indicate delay of absorption rate [Jenkins et al., 1995], it remains unclear whether such absorption delay is the result of reduced gastric emptying or hormonal changes. In addition, plasma insulin which is helpful in further understanding the mechanism by which North American ginseng causes postprandial hypoglycemia was
human trial for future studies on the application of *P. quinquefolius* in the management of NIDDM, future clinical trials should aim at elucidating the mechanism of ginseng’s action by first determining whether ginseng reduces glucose absorption by slowing gastric emptying or by acting on the endocrine system.

Several factors need to be considered when accounting for a delay in gastric emptying. Each gelatin capsule in this study contained either 490 mg or 500 mg ginseng powder. Therefore, the doses of 3 g, 6 g, and 9 g of ginseng used in this study (Section 2.3.2) was consistent of 7, 13, and 19 capsules respectively. As a result, the bulk of the material may have caused the delay in postprandial glucose absorption by slowing gastric emptying. However, there was no significant difference between 3 g, 6 g, and 9 g ginseng powder in lowering postprandial blood glucose despite their differences in material bulkiness. (Figure 4.1). As a consequence, the material bulkiness of the capsules is unlikely to be an important factor. In order to further illustrate this in future experiments, xylose can be given together with ginseng to compare its urinary levels before and after each test to that of controls with no ginseng. A reduced urinary xylose output tends to correspond with a slower mouth-to-cecum transit time [Jenkins et al., 1978], and thereby indicates delayed gastric emptying. Thus, if there is no change in urinary xylose levels between ginseng-treated and untreated meals, there is no slowing of gastric emptying associated with North American ginseng. Lactulose can also be used to determine whether gastric transit time is delayed [Jenkins et al., 1978] by comparing breath gases from lactulose control, glucose alone with lactulose and ginseng treatment with lactulose.
of North American ginseng. Although the exact mechanism is not understood, it is postulated that it is related to its effects on the hypothalamus during stressful situations (Section 1.2.6). As a consequence, it remains unclear how ginseng elicits its pharmacological effects. The use of radio-labeled glucose may be useful in understanding the mechanism by which North American ginseng improves overall glucose both normal and NIDDM individuals. In addition, future studies may also need to measure other blood parameters in addition to glucose. For example, insulin, free fatty acids, HDL, LDL, triglycerides, cortisol, glucagon, and catecholamines measurements can all shed light in understanding the mechanism.

There are many different species of *Panax* known to exist (Table 1.5). Besides, there are other plants which have similar appearance as *Panax* species but are botanically different. Furthermore, some of the ginseng components vary in quantities depending on the year of growth (Table 1.7) which may affect potency of the ginseng. It has been illustrated that certain GS are of highest quantity at four or five year of growth [Zhang et al., 1980]. As a consequence, it is important for future that the particular variety of ginseng chosen is, in fact, *P. quinquefolius* and that they are selected from the same manufacturer batch of four to five year-old roots. It may also be necessary to assay certain ginseng components and determine the nutrient profile of any new supplies of ginseng so that ginseng material can be better standardized. For more consistent ginseng materials, standardized ginseng extracts may also be useful in ensuring potency.
and diabetic humans, a similar protocol can be used to test the effectiveness of other Panax species with similar year of growth in the lowering of postprandial glycemia. In addition, the optimal time and dose of administration of each species and their possible mechanism of action can also be determined. As a result, in the future it may be possible to rank different Panax species of ginseng in order of effectiveness. Long-term human trials with NIDDM patients can also give light to the possibility of including North American ginseng powder in overall NIDDM management.

5.2 General conclusion

The overall objective was to determine if North American ginseng powder could lower postprandial blood glucose response. North American ginseng taken together with a glucose challenge did not lower postprandial glycemic response, while ginseng taken at any given dose with given time prior to the glucose load greatly reduced postprandial blood glucose response. This indicated that ginseng might elicit its postprandial blood glucose lowering effect by certain pharmacological pathways, instead of altering the physical nature of food substances to entrap nutrients.

The results of this study also suggested that P. quinquefolius (3 g, 6 g, 9 g) lowered postprandial glycemia when it was taken either at 40 or 80 minutes prior to the glucose challenge. In addition, at a high dose of 9 g ginseng taken at 120 minutes prior to the glucose load also produced a similar reduction in postprandial blood glucose. This suggests that the dose levels selected in this study may be too high to detect the
ginseng administration by developing dose curves from 0 to 3 g and at determining the optimal time of ginseng administration.
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APPENDIX
INTRODUCTION

Ginseng is a man-shaped root indigenous to Asia, North America and Russia. Its value in promoting overall body health has long been recognized by the Chinese as precious and renowned. In fact, they have been using ginseng for more than 5,000 years. Ginseng has traditionally been thought to prolong life, boost energy, elevate sex drive and soothe base emotions. Over the years, many other conditions, including diabetes, have been reported to be alleviated by the constant consumption of ginseng. However, these claims are generally based upon anecdotal evidence. Therefore, the purpose of this study is to investigate the efficacy of North American ginseng in normal humans and to determine the time and dose of administration.

PROCEDURES

Phase I:

This phase consists of 12 individual tests in which each test lasts for a maximum of 3.5 hours. In each test, I will be asked to come to the Clinical Nutrition and Risk Factor Modification Centre, 61 Queen Street East after a 10-12 hour-overnight fast. I will give seven capillary blood samples in each test. Each sample requires 3-5 drops (1/4 tablespoon) of blood.

When I reach the Clinic, I will give a fasting finger prick capillary blood sample. Then, I will ingest either 3, 6, or 9 g (7, 13, 18 capsules) of North American ginseng powder contained in gelatin capsules / 120, 240, or 360 mg (4, 8, or 12 capsules) of North American ginseng extract contained in soft gel capsules with 250-400 mL water in 10 minutes. After either 40, 80, or 120 minutes, I will give yet another finger prick capillary blood sample.

I will then take an oral orange glucose drink consisting of 100 mL Glucodex® (DIN 00509965) and 150 mL water. This drink contains 25 g glucose. Once again, I will collect finger prick capillary blood at 15, 30, 45, 60 and 90 minutes after consuming the glucose drink. The blood samples will be analyzed for glucose levels.
This phase consists of 2 individual tests in which each test lasts for a maximum of 2.5 hours. In each test, I will be asked to come to the Clinical Nutrition and Risk Factor Modification Centre, 61 Queen Street East after a 10-12 hour-overnight fast. I will give 8 venous blood samples in each test. Each sample requires 30 mL (2 tablespoons) of blood.

When I reach the Clinic, I will give a fasting venous blood sample. I will consume either 3, 6, or 9 g (7, 13, or 18 capsules) of North American ginseng powder contained in gelatin capsules / 120, 240, or 360 mg (4, 8, or 12 capsules) of North American ginseng extract contained in soft gel capsules with 250-400 mL water in 10 minutes with 250 - 400 mL water.

After either 40, 80, or 120 minutes, I will give another venous blood sample. I will then drink an oral orange glucose drink contain 100 mL Glucodex® (DIN 00509965) and 150 mL water. This drink has 25 g glucose.

Venous blood sample will be taken at 15, 30, 45, 60, 90, and 120 minutes after the ingestion of the orange drink. The venous blood samples will be analyzed for hormones and lipids.

RISKS

There are no known risks from ginseng powder and extract. However, minor discomfort is expected when the needle is inserted into my vein. Bruising may occur when the needle is removed but this can be prevent by keeping pressure on the site for 3-5 minutes after the removal of the needle. If bruising occurs, it will go away in 2-3 days.

BENEFITS

I may expect to benefit from this study in the following ways: my blood sugar, blood lipids, blood hormones may improve. I will receive the benefits of evaluation of symptoms and general health discussions with the doctor and help in finding additional treatment if needed. I will have a chance to contribute to a study which may be of benefit to people in the future.

CONFIDENTIALITY

The results from the study will be confidential. My results will not be shown to anyone, unless required by law, with my written permission. My results will be sent to my physician if I wish.
I understand that the study investigator may stop my being in the study at any time without my consent. My participation may be discontinued if the study investigator judges that this is in my best interest or if I fail to comply to study procedures.

QUALIFICATIONS

I understand I cannot be in this study if I abuse alcohol or drugs, or if I have a serious illness which is not under control. I am above the age of 18 years.

CONSENT

I have read this consent form, have had all my questions about the study answered, and believe I know what will happen to me if I agree to be a part of the study. I understand that I may reach Dr. Vladimir Vuksan at (416) 867-7450 if I have further questions pertaining to the study.

I may quit at any time. If I decide not to participate or quit, I will not be penalized and will not give up any benefits of which I had before entering the study. If I decide not to participate or quit, I will notify the study investigator. I have received a copy of this consent form.

Volunteer's Name: ..............................................................................................................

Volunteer’s Signature:........................................ Date: ...........................................................

Investigator’s Name: ........................................ Date: ...........................................................

Investigator’s Signature:............................... Date: .............................................................