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Ginseng for the Treatment of Diabetes and Diabetes-related Cardiovascular Complications. A Discussion of the Evidence

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Abstract

Diabetes mellitus is a chronic metabolic disorder associated with elevated blood glucose levels due either to insufficient insulin production (Type 1 diabetes) or to insulin resistance (Type 2 diabetes). The incidence of diabetes around the world continues to rise dramatically with more than 400 million cases reported today. Among the most serious consequences of chronic diabetes include cardiovascular complications which can result in both cardiac and vascular deleterious effects. Although numerous treatment options are available for treating diabetes, both pharmacological and non- pharmacological, there is substantial emerging interest in the use of traditional medicines for the treatment of this condition and its complications. Among these is ginseng, a medicinal herb which belongs to the genus *Panax* and which has been used for thousands of years as a medicinal agent especially in Asian cultures. There is emerging evidence from both animal and clinical studies that ginseng, ginseng constituents including ginsenosides and ginseng-containing formulations can produce beneficial effects in terms of normalization of blood glucose levels and attenuation of cardiovascular complications through a multiplicity of mechanisms. Although more research is required, ginseng may offer a useful therapy for the treatment of diabetes as well as its complications.

Keyword:

Ginseng , diabetes , cardiovascular complications

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition which is characterized by a sustained elevation in plasma glucose concentrations. There are two primary causes of DM, either insufficient production of insulin by the beta cells of pancreas (Type 1 DM) or the development of insulin resistance which may also be associated with deficient insulin production (Type 2 DM). The latter represents the vast majority of the more than 400 million cases of DM worldwide today with the incidence of DM expected to rise dramatically over the next 20 years (Shi and Hu 2014, summarized in Table 1). Although the treatment of Type 1 DM involves insulin administration, there are a greater number of treatment options for Type 2 DM in addition to pharmacological interventions including lifestyle modification consisting of weight loss, exercise and dietary modification. Thus, Type 2 DM is therefore considered a lifestyle-related disease closely associated with increased incidence of obesity, inactivity and poor dietary habits. The existence of DM including the distinction between the two types of DM has been known for thousands of years with diabetes being first described by the Egyptian physician Hesy-Ra around the year 1552 BC (King and Rubin 2003). Much of the increase in the worldwide incidence of DM seen today can be attributed to the increase in the incidence of Type 2 DM. This can be seen as well in economically emerging countries such as China as these countries increasingly embrace western lifestyle habits (Yang et al. 2010a). It is now recognized that DM represents a global medical problem and not one restricted exclusively to western developed nations. In fact, according to a recent report it has been estimated that there were 108 million adults with DM in 1980 which has increased to 422 million in 2014 (NCD Risk Factor Collaboration 2016). This increase was attributed to a number of factors including both prevalence and population growth

as well as interaction between these two factors (NCD Risk Factor Collaboration (NCD-RisC). 2016).

Treatment options for DM

DM was considered to be a fatal disease until the discovery of insulin by Canadian researchers Frederick Banting and Charles Best at the University of Toronto in 1921-1922 and insulin administration continues to be the primary treatment for Type 1 DM (Polonsky 2012). For readers interested in the history of the discovery of insulin an outstanding and highly readable account of this event by Canadian historian Michael Bliss can be recommended (Bliss 1982).

Type 2 DM can be treated with various options including, as mentioned above, non-pharmacological approaches such as lifestyle modification including exercise, weight loss and dietary management. The mainstay of pharmacological therapy for Type 2 DM for many years and which remains first-line therapy is metformin. Although its mechanisms of action are not fully understood, the therapeutic effect of metformin is thought to be based on suppressing hepatic gluconeogenesis and enhancing insulin sensitivity likely related to activation of the enzyme AMP-activated protein kinase (AMPK). However, other mechanisms for the beneficial effects of metformin, especially related to cardiovascular health, are also likely involved which may not be directly related to improved glucose utilization (Papanas et al. 2009). Various other medications are also available, some recently introduced, which provide a number of additional options for the treatment of Type 2 DM and which can be reviewed elsewhere (Tahrani et al. 2016).

Targeting DM-related cardiovascular complications

Although uncontrolled DM is associated with numerous health risks, increased cardiovascular risk and development of cardiovascular complications remain among the most important as they have a major negative impact on life expectancy (Grundy et al. 1999). Moreover, cardiovascular consequences of DM, such as coronary heart disease, are sometimes difficult to identify as this can occur in the absence of symptoms (Wingard et al. 1993). Many of the cardiovascular complications in DM reflect changes to vascular integrity particularly the development of vascular remodelling resulting in organ damage or the complications may be related to direct effects on the myocardium (Figure 1). Vascular complications may reflect initial micro RNA-dependent damage to the vascular endothelium resulting in vascular changes (Cao et al. 2014). There is a general agreement that oxidative stress represents a major contributing factor to numerous cardiovascular complications arising from DM (Kayama et al. 2015). Changes in vascular integrity including arterial calcification are thought to be the prime causes of many cardiovascular pathologies including heart disease such as cardiomyopathy, kidney disease, diabetic retinopathy as well as increased risk of stroke (Craeger et al. 2003; Harper et al. 2016). In terms of cardiomyopathy, there is evidence that diabetic conditions can directly adversely affect organ function independently of coronary vascular effects through a host of potential mechanisms directly affecting myocardial performance (Wan and Rodrigues 2016; Miki et al. 2013).

The potential for new therapies including herbal medications and other natural products to reduce cardiovascular complications from DM can be based on two primary goals. The first would be to reduce the hyperglycemia burden *per se* by either improving insulin production by the pancreatic beta cells whereas the second would be a more specific approach involving direct targeting of cardiovascular tissues. However, it can be relatively difficult to separate the two

effects especially when dealing with drugs that have antidiabetic effects as this itself could indirectly reduce cardiovascular consequences of DM.

Experimental models for the study of DM

There is a number of experimental approaches which are widely used for the study of DM, its underlying mechanisms, and the development of new therapeutic strategies. Among the simplest is the use of isolated or cultured cells which can then be exposed to high glucose concentrations for varying periods of time. The direct effects of hyperglycemic conditions on cell function and integrity have been studied extensively and demonstrate that this can initiate a plethora of cell signaling changes resulting in phenotypic alterations including hypertrophy and cell injury through both necrosis and apoptosis. Modification of these responses, therefore, represents a useful tool particularly for initial screening of potential therapeutic agents.

Various animal models are also available for the study of both Type 1 and Type 2 DM. With respect to the former, among the most widely used is the streptozotocin (STZ) model. STZ is a glucosamine-nitrosourea compound which was originally developed as an anti-cancer agent and which causes pancreatic beta cell death *via* different mechanisms but primarily by fragmenting DNA. It can produce Type 1 DM relatively rapidly and, in some cases, only after a single administration although both the actual dose and the number of administrations are generally determined by various factors such as animal species (Szkudelski 2001). Another widely used Type 1 DM model is one produced by administering alloxan, which destroys pancreatic beta cells primarily by generation of reactive oxygen species (Szkudelski 2001).

Various animal models of Type 2 DM also exist primarily involving the use of genetically-modified mice many of which are animal models of obesity with accompanying insulin

resistance thus reflecting, to a large degree, the condition found in humans. Among these are the *ob/ob* mouse which is deficient in leptin, a 16 kDa protein produced primarily by white adipocytes and which plays an important role as a satiety factor by its direct action on the hypothalamus. In contrast the *db/db* mouse is also related to leptin dysfunction produced not by leptin deficiency but instead by a mutation of the leptin receptor thus preventing the satiety effect of the protein resulting in obesity. Similarly, the JCR-LA-cp rat, which also has non-functional leptin receptors due to an autosomal recessive mutation, has proven useful for the study of diabetes associated with insulin resistance and obesity and the development of cardiovascular disease (Pierce et al. 1997). Indeed, leptin dysfunction due either to deficiency in leptin production or mutation of the leptin receptor constitutes a major basis for the development of animal models of Type 2 DM (Wang et al. 2014). Other rat models include the spontaneously obese *fa/fa* Zucker rat and the Goto-Kakizaki rat which develops Type 2 DM in the absence of obesity. Thus, there is no shortage of experimental models to assess the potential influence of therapeutic interventions. The subject of animal models for the study of diabetic complications has recently been reviewed (Betz and Conway 2016).

Ginseng and its constituents as antidiabetic agents: possible underlying mechanisms

As noted above, the potential benefit of ginseng and ginseng related products on cardiovascular complications associated with DM may reflect either a hypoglycemic effect or direct protective effect on the cardiovascular system independently of blood glucose concentrations. Indeed, with respect to hypoglycemic effects, ginseng and many other natural products and herbals have been shown to have insulin-like activities to varying degrees which would make them effective for the

treatment of Type 2 DM (Broadhurst et al. 2000; Shapiro and Gong 2002; Hui et al. 2009; Yuan et al 2012). The potential benefit of ginseng as a hypoglycemic agent was indeed demonstrated in alloxan-induced diabetic mice treated with a ginseng extract, an effect attributed to increased release of insulin release from the pancreas and which was shown to be independent of saponin content (Kimura et al. 1981a, 1981b). This supports the concept that the hypoglycemic effect of the ginseng extract is not solely due to the saponin constituents but also to other bioactive ginseng components (Ng and Yeung 1985). Among these is the polysaccharide fraction designated as DPG-3-2, which has been shown to reduce hyperglycemia in a genetic mouse model of DM, but which had no effect when administered to normal mice (Ng and Yeung 1985; Waki et al. 1985). As discussed below, various constituents of ginseng, particularly ginsenosides and polysaccharides account for antidiabetic effects and in some cases such as with respect to *P. quinquefolius* (also known as North American ginseng), it appears that both ginsenosides and polysaccharides can contribute to the reduction in plasma glucose levels in diabetic animals (Xie et al. 2002a, 2004a). There is also evidence that polysaccharides and at least one ginsenoside, Rb1, exhibit synergistic hypoglycemic effects when studied in a rat model of Type 2 DM (Li et al., 2018). There is some evidence that Korean red ginseng, which is basically fresh Asian ginseng (*P. ginseng*) subjected to a steaming-drying protocol exerts more robust hypoglycemic effects due to biotransformation of its bioactive constituents. The concept of subjecting ginseng to steaming protocols is discussed in greater detail in the following section.

There is a plethora of proposed mechanisms for the insulinotropic and other antidiabetic actions of ginseng which have been proposed including inhibition of cytokine-induced apoptosis of pancreatic-insulin producing beta cells, likely *via* multiple mechanisms. For instance, addition of a *P. quinquefolius* extract, which also improves metabolic status in diabetic obese Zucker rats

(Banz et al. 2007), inhibited production of pancreatic beta cell mitochondrial uncoupling protein-2 (UCP-2), (Luo and Luo 2006), a protein associated with diminished insulin release (Chan et al. 1999). The reduction in UCP-2 was found to be associated with increased insulin production as well as reduced apoptosis produced by IL-1 β administration thus preserving beta cell integrity (Luo and Luo 2006). In addition, a *P quinquefolius* alcoholic root extract has been shown to increase insulin production and improve insulin sensitivity in Type 1 and Type 2 DM models, respectively (Sen et al. 2013a). Other potential mechanisms for the beneficial effect of ginseng may lie in its ability to alter intestinal glucose absorption. This has been proposed as a mechanism for the antidiabetic effect of Radix ginseng when administered for four weeks to KKAy mice, a genetic obesity model of Type 2 DM caused by disruption of the hypothalamic melanocortin-4 receptor resulting in hyperphagia (Huszar et al. 1997). Ginseng treatment was associated reduced intestinal glucose absorption and inhibition in adipocyte glucose-6-phosphatase through a mechanism involving upregulation of adipocyte peroxisome proliferator-activated receptor gamma (PPAR γ), a nuclear receptor protein functioning as a transcriptional which plays an important role in fatty acid and glucose metabolism (Chung et al. 2001). This ability to activate PPAR γ has also been demonstrated using cultured adipocytes treated with the ginsenoside insenoside 20S-protopanaxatriol (Han et al. 2006). Indeed, PPAR γ agonists such as thiazolidinediones are useful for the treatment of Type 2 DM by increasing glucose utilization (Rizos et al. 2016). However, other mechanisms are likely also involved with respect to modulation of fatty acid metabolism by ginseng. For example, alcoholic extracts from both *P quinquefolius* (extracted in 80% ethanol) and Korean ginseng (extracted in 50% ethanol) were able to mimic the antilipolytic effect of insulin on adipocytes through a mechanism involving phosphodiesterase 3 and 4 activation albeit through different cell signalling mechanisms from

insulin (Wang et al. 2006). Although the active antilipolytic ginseng constituent was not identified in that study, it is interesting that none of the ginsenosides, including Rb1, Re, Rg1, Rc, Rb2, and Rd had any effect when studied individually (Wang et al. 2006). A potential role for increased secretion of glucagon-like peptide-1 (GLP1), an intestine-derived incretin which increases insulin release and sensitivity, has been proposed as a mechanism for the antidiabetic effect of ginseng saponins in low dose STZ rats fed a high fat diet (Liu et al. 2013a). Thus, the administration of this preparation for twenty-eight days produced a reduction in glucose levels in these animals, an effect associated with increased plasma GLP1 levels and increased GLP1 tissue expression. Moreover, the effect of a total saponin preparation on increased GLP1 production was mimicked by ginsenosides Rb1, Rb2, Rc and Rd when added to cultured human NCI-H716 cells (derived from colorectal adenocarcinoma) although ginsenoside Re was without effect (Liu et al. 2013a).

The antidiabetic effect of ginseng appears to be represented in all its components. However, there is evidence that the reduction is more prominent in the berry versus root extract (Dey et al. 2003) although a leaf extract of *P. quinquefolius* has also been shown to exert a hypoglycemic effect when administered to *ob/ob* mice. An alcoholic berry extract from Korean ginseng may also be beneficial for treatment of increased insulin resistance seen with aging. In this regard, administration of this preparation to aged (15 months old) mice was associated with improved insulin sensitivity and a reduction in pancreatic islet hypertrophy (Seo et al. 2015). The improvement in insulin sensitivity was associated with increased muscle protein levels of tyrosine phosphorylated insulin receptor substrate (IRS)-1, protein kinase B (AKT), as well forkhead box protein O1 (FOXO1) and peroxisome proliferator-activated receptor gamma (PPAR γ) which are known as aging- and insulin resistance-related factors (Seo et al. 2015). A

similar benefit in improving insulin sensitivity was shown with fermented Korean ginseng when administered for sixteen weeks to aged *ob/ob* mice (Cheon et al. 2015).

It is interesting that a contributing factor dictating the beneficial effects of ginseng, at least with respect to *P. ginseng* (also known as Asian ginseng), may be the age of the ginseng itself with older varieties (4 or 6 years) showing better efficacy as antidiabetic agents than younger varieties (Hu et al. 2011). It has been proposed that these age-dependent effects may be due to changes in absolute content or ratios of bioactive compounds which account for the antidiabetic influence of ginseng (Hu et al. 2011).

Ginseng-containing formulations have also been shown to exert a hypoglycemic effect in DM animal models. Among these is Jiang-Tang-Ke-Li, a *P. ginseng* containing formulation which reduced plasma glucose concentrations in fructose fed diabetic rats, an effect in fact mimicked by *P. ginseng* administration, which was attributed to improvement in insulin resistance in these animals (Wang et al. 2003).

Does steaming ginseng provide superior antidiabetic properties?

As already noted above, there is evidence that ginseng subjected to a heating process provides substantial antidiabetic properties which may be superior to that found with non-heated ginseng varieties. The beneficial effect of steamed ginseng likely reflects the formation of novel ginsenosides due to the heating process which is suggested to offer superior therapeutic benefit (Kim et al., 2000a). Korean red ginseng for example diminishes pancreatic beta cell apoptosis resulting in increased insulin release (Kim and Kim 2008) potentially acting through a ginsenoside-dependent inhibition of reactive oxygen species and nitric oxide formation (Kim et al. 2008; Kim et al. 2007). While this suggests a role for reactive oxygen species, it is interesting

that administration of an antioxidant to *ob/ob* mice failed to produce antidiabetic effects (Xie et al. 2009). Importantly, the anti-apoptotic of red ginseng on a pancreatic beta-cell line was found to be more pronounced with red ginseng as compared to white ginseng (Kim and Kim 2007). In addition, improvement in insulin sensitivity by Korean red ginseng has also been demonstrated in Type 2 DM models when administered to genetically obese rats, an effect associated with increased fatty acid oxidation due to AMPK activation (Lee et al. 2009) as well as reduced mitochondrial damage and inflammation in skeletal muscles (Park et al. 2018). Korean red ginseng can also improve Type 1 DM in STZ-treated mice, an effect associated with improved immune function in these animals (Hong et al. 2012). It is interesting that although increased angiogenesis represents a potentially important process for ginseng-induced cardiovascular benefit, it is possible that inhibition of angiogenesis may represent a potential basis for its antidiabetic effects, at least with respect to Korean red ginseng. In this regard, thirteen-week treatment of female *db/db* mice with Korean ginseng produced various beneficial effects including a reduction in adipocyte size in peripheral adipose tissue (Lee et al. 2014). The latter was attributed to reduced angiogenesis possibly due to downregulation of vascular endothelial growth factor or VEGF (Lee et al. 2014).

Although Korean red ginseng exerts antidiabetic effects, black ginseng, a relatively new ginseng which is produced by subjecting white ginseng to up to nine cycles of steaming and drying for approximately three hours, appears to exert superior benefit when compared to red ginseng in a STZ mouse model (Kim et al. 2016). This was attributed to altered ginsenoside content in the black ginseng extract, specifically the presence of ginsenoside Rg5 and compound K (20-O-beta-d-glucopyranosyl-20(S)-protopanaxadiol), a highly active metabolite not normally found in ginseng, but which can be produced through biotransformation reactions (Kim et al. 2016; Yang

et al. 2015). However, using an *in vitro* approach, black ginseng was shown to significantly increase glucose uptake through AMPK, Sirt1 and PI3-K pathways although this was attributed primarily to the presence of ginsenoside Rh4 (Seo et al. 2016). Irrespective of the identification of the precise constituent responsible for beneficial effect of black ginseng, a somewhat similar mechanism was demonstrated *in vivo* using *db/db* mice where the hypoglycemic effect of black ginseng was shown to be associated with suppression of hepatic gluconeogenesis *via* AMPK activation as well as improved glucose utilization due to upregulation of both GLUT2 and GLUT 4 transporters in muscle tissue (Kang et al. 2017).

Ginsenosides and other ginseng constituents as antidiabetic agents

Ginsenosides

Based on current evidence it appears that numerous ginseng components account for the antidiabetic effects of ginseng. As already alluded to, alcoholic extracts of ginseng have demonstrated beneficial effects in animal diabetes models. A saponin preparation from *P notoginseng* containing notoginsenoside R1 as well as ginsenosides Rd, Re, Rg1, Rg2, Rh1 and Rb1 increased glucose utilization in cultured 3T3-L1 cells (Kim et al. 2009a) which could occur, at least with respect to ginsenoside Rg1, *via* AMPK activation (Lee et al. 2012). In addition, a complex of ginsenosides Rk1 + Rg5 has been shown to increase glucose utilization in cultured cells exposed to endoplasmic reticulum stress (Ponnuraj et al. 2014). Ginsenoside have also been demonstrated to reduce blood glucose levels, severity of obesity and metabolic disturbances associated with the diabetic state produced by various factors including STZ administration, high fat diet consumption as well as genetic models of DM (Liu et al. 2009, 2013a, 2013b; Xie et al. 2004b; Yun et al. 2004, 2007; Chen et al. 2008). Extracts of unique ginsengs such as mountain

ginseng adventitious roots which had been grown through tissue culture exert antidiabetic effects in STZ rats and are rich in a large number of ginsenosides including Rb1, Rb2, Rc, Rd, Rg3 as well as Rh2 (Murthy et al. 2014). Moreover, individual ginsenosides such as Rb1, Rb2 and GRe also exert a hypoglycemic effect in diabetic mouse and rat models (Yang et al. 2010b; Yokozawa et al. 1985; Quan et al. 2012; Xie et al. 2005) with the beneficial effect ginsenoside Re persisting for up to three days following cessation of treatment in the *ob/ob* mouse model (Xie et al. 2005). The ginsenoside Rh2 was shown to acutely decrease blood glucose concentrations in non-diabetic rats (Lee et al. 2006) as well as in rats subjected to STZ-induced DM (Lai et al. 2006) potentially by increasing insulin release as a result of activation of pancreatic beta cell muscarinic receptors (Lee et al. 2006; Lai et al. 2006). In addition, ginsenoside Rh2 has been shown to improve insulin sensitivity when administered to insulin resistant rats produced by a high fructose diet (Lee et al. 2007). Moreover, at least one ginsenoside, Rg3, has been shown to protect pancreatic beta cells by reducing apoptosis produced by exposure to high levels of fatty acids or a cytokine cocktail (Kim et al. 2010b; 2014). With respect to ginsenoside Rb2, it has also been shown to blunt the reduction in hepatic albumin mRNA seen in STZ-induced diabetic rats thus suggesting a potential effect on improving mRNA stability in DM (Yokozawa et al. 1996). Moreover, Rb2 appears to directly inhibit hepatic gluconeogenesis *via* AMPK activation (Lee et al. 2011).

Several ginseng species administered in many forms including berry juice and extract have been shown to reduce blood glucose levels in diabetic obese *ob/ob* and *db/db* mice (Xie et al. 2002a, 2002b, 2007), an effect, at least with respect to *P. quinquefolius* attributable to ginsenoside Re and likely other ginsenosides as well (Attele et al. 2002). Some ginsenosides have been shown to directly inhibit apoptosis of pancreatic beta cells, among them ginsenosides Rb1 and Rg1, by

inhibiting pro-apoptotic signalling (Chen et al. 2012). Another potential mechanism has been proposed to involve stimulation of insulin receptor substrate 2, a cytosolic signalling protein important for pancreatic beta cell survival (Park et al. 2008). In that study, ethanolic extracts of *P. ginseng*, as well as other herbal medications, were used to determine beneficial effects although the precise ginsenosides in the *P. ginseng* extract were not identified (Park et al. 2008).

Polysaccharides

Polysaccharides as well have been shown to exert salutary effects as borne out by data showing that a number of aqueous extracts of ginseng and polysaccharide fractions exert hypoglycemic effects which may be more pronounced in the acidic polysaccharide fraction (Xie et al. 2004a, Konno et al. 1985; Oshima et al. 1985, 1987; Sun et al. 2014). Moreover, ginseng treated with the enzyme pectinase has been shown to express a markedly reduced ginsenoside content although the hypoglycemic effect of this preparation was enhanced when administered to high fat diet-induced hyperglycemic mice (Yuan et al. 2011a). The benefit was attributed to the presence of the ginsenoside metabolite IH-901 (compound K). Indeed, as discussed below, compound K has been shown to exert potent antidiabetic effects in a variety of experimental models.

Compound K

Compound K has been shown to have glucose lowering effects when administered to *db/db* mice relatively equal to that seen with metformin both on glucose levels as well as on other indices of metabolism (Yoon et al. 2007). Interestingly, the combination of compound K plus metformin provided some indices of synergy, suggesting the potential usefulness of compound K, and indeed ginseng in general as adjunctive therapy in combination with standard medications for the

treatment of Type 2 DM (Yoon et al. 2007). The salutary effect of compound K in improving insulin resistance has been linked to the activation of PI3K/Akt signaling (Jiang et al. 2014; Yuan et al. 2011b). In addition, the anti-diabetic effects of compound K has been linked to numerous other beneficial metabolic effects including enhancing insulin secretion *via* activation of ATP-sensitive K⁺ channels as well as improving insulin secretion (Han et al. 2007).

Compound K can produce other salutary effects as well including the inhibition of pancreatic beta cell apoptosis, which can also contribute to its antidiabetic effect (Kim et al. 2009b). The antiapoptotic effect of compound K was proposed to involve the activation of the stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK/JNK) pathway (Li et al. 2012). However, compound K can also suppress key hepatic gluconeogenesis enzymes including phosphoenolpyruvate carboxykinase, glucose-6-phosphatase as well as AMPK in type 2 diabetic mice (Li et al. 2012; Wei et al. 2015) and can increase the expression levels of the glucose transporter isoform-2 (GLUT2) in cultured pancreatic beta cells (Gu et al. 2013) which, when taken together, can further explain the hypoglycemic effect of this ginseng metabolite.

Modulation of DM-related cardiovascular complications by ginseng

In addition to potential cardiovascular benefit due to improved insulin production and utilization, there is also evidence that ginseng-related products can also offer benefit *via* direct effects on cardiovascular responses or by reducing cardiovascular risk factors such as obesity (Li et al. 2014a) or the inflammatory response as has been shown for ginsenoside Re when administered to STZ diabetic rats (Cho et al. 2006). Indeed, inhibition of the inflammatory response may be an underlying general mechanism for the beneficial effects of a variety of Traditional Chinese Medicines including ginseng for the treatment of diabetes related disorders (Xie and Du 2011).

While various mechanisms likely underlie the direct cardiovascular benefit associated with ginseng, the extensive evidence showing antioxidant properties of this herb suggests that this may be an important contributing factor (Jung et al. 2005). From *in vitro* studies, there is substantial evidence that oxidative stress-mediated cardiovascular dysfunction is produced by hyperglycemia *per se* which triggers the formation of reactive oxygen species. For example, cultured human vascular endothelial cells (HUVECs) exposed to intermittent (alternating every 24 h) high glucose concentrations (25 mM vs 5.6 mM control) for eight days demonstrated loss of cell viability and increased oxidative stress which was attenuated by a *P. quinquefolius* saponin leaf and stem extract, an effect attributed to activation of the PI3K/Akt/GSK3 β pathway (Wang et al. 2013). Other mechanisms may also mediate ginseng-induced vascular protection in DM. For example, *P. ginseng* extract administration to STZ diabetic rats restored endothelial dependent aortic relaxation *ex vivo*, an effect attributed to a reduced upregulation in aortic expression of various atherosclerosis-related genes including adhesion molecules and various cytokines (Chan et al. 2013).

Diabetic cardiomyopathy and ischemic heart disease

Among the well-documented cardiovascular consequences of chronic DM is the development of heart failure, secondary to the development of diabetic cardiomyopathy. The basis for diabetic cardiomyopathy is exceedingly complex but involves numerous metabolic and cellular derangements, such as the excess formation of non-esterified fatty acids which can trigger key cell signalling mechanisms resulting in hypertrophy and cell death independently of the development of coronary atherosclerosis (Poornima et al. 2006; Miki et al. 2013; Wan and Rodrigues 2016;). Moreover, glucose, acting through various cell signalling processes can produce the cardiomyopathy phenotype (Mortuza and Chakrabarti 2014). High glucose

concentrations can directly trigger the hypertrophic response, a process likely mediated by factors such as endothelin-1 and leptin (Chen et al. 2007; Majumdar et al. 2009). Treatment of Type 1 STZ-mice or Type 2 *db/db* mice with *P. quinquefolius* alcoholic extract reduced the degree of cardiomyopathy as shown by diminished indices of oxidative stress and extracellular matrix proteins while enhancing left ventricular function in these animals (Sen et al. 2012, 2013b). In addition, cardiac function has been shown to be improved in STZ-treated rats administered ginseng for a seven-day period which was attributed to upregulation of myocardial PPAR δ expression (Tsai et al. 2014). Moreover, administration of a ginseng containing preparation mixture of Shengmai plus Danshen has been shown to reduce this type of injury in diabetic rats as demonstrated by reduced collagen fiber content, apoptosis and the expression levels of various proinflammatory cytokines (Ni et al. 2011).

Individual ginsenosides may also exert beneficial effects in terms of reducing diabetic cardiomyopathy. For example, ginsenoside Rh2 administration for 28 days to STZ-treated rats showed substantially improved cardiac function which associated with diminished fibrosis (Lo et al. 2017). Moreover, Rh2 reduced the production of reactive oxygen species when administered to cultured H9c2 cells exposed to high glucose conditions (Lo et al. 2017). These beneficial effects of Rh2 were attributed to activation of PPAR δ signalling pathways (Lo et al. 2017).

There is extensive evidence that DM is associated with increased risk of ischemic heart disease and that hearts from diabetic animals are sensitized to ischemic insult (Paulson 1977) although decreased sensitivity has also been reported (Tani and Neely 1988). From a general perspective there is emerging evidence that ginseng, and indeed other Chinese natural products can protect the heart and other organs against ischemic and reperfusion injury (Han et al. 2017).

Administration of ginseng or ginseng related products may therefore reduce the potential

increased risk of ischemic myocardial injury in diabetic subjects. Indeed, treatment of diabetic rats with ginsenoside Rb1 prior to induction of 30 minutes of coronary artery occlusion followed by 120 min reperfusion resulted in reduced degree of apoptosis and infarct size, protective effects attributed to activation of the phosphatidylinositol 3-kinase-Akt salvage pathway (Wu et al. 2011).

Diabetic retinopathy

Diabetic retinopathy is a major complication of DM and a leading cause of blindness. The causes of diabetic retinopathy are complex and involve microvascular complications due to endothelial dysfunction as well as numerous cellular, molecular, and functional alterations occurring in many types of retinal cells (Cai and McGinnis 2016). There is evidence that ginseng and ginseng-related products may attenuate the degree of diabetic retinopathy in a number of animal models of DM. For example, the degree of retinopathy was substantially reduced by treating STZ-treated mice or *db/db* mice with an alcoholic extract of *P. quinquefolius* likely *via* reduction in oxidative stress (Sen et al. 2013b). In addition, administering a concoction of an aqueous extract of *Radix Astragali*, *Radix Angelica sinensis* and *P. notoginseng*, which is widely used as a Traditional Chinese Medicine, substantially reduced the degree of retinopathy as shown by reduced leukostasis, acellular capillaries and vascular leakage, when given to either STZ-treated rats or Goto-Kakizaki rats which was associated with markedly decreased levels of proinflammatory factors (Gao et al. 2013). Moreover, this preparation prevented glucose-induced inhibition of endothelial cell migration and proliferation *in vitro* (Gao et al. 2013). Modulation of gene expression may also be involved in the protective effect of ginseng against diabetic retinopathy. Indeed, microarray analysis of retinas from STZ diabetic rats revealed more than 300 gene alterations with upregulation of 268 genes and downregulation of 58 genes

with more than 80 alterations markedly attenuated by Korean ginseng administration (Yang et al. 2016). Some of these changes such as the gene encoding for Glial fibrillary acidic protein are known markers associated with diabetic retinopathy suggesting that inhibition of these changes contributes to the beneficial of Korean ginseng and perhaps other ginseng varieties as well.

Ginsenosides have also been proposed as possible inhibitors of diabetic retinopathy based on *in vitro* studies. For example, ginsenoside Rg1 has been studied using cultured retinal Müller cells exposed to hyperglycemic (25 mM glucose) conditions for 48 hours. These cells express high degree of mesenchymal activity and are a major source of fibrosis. Rg1 has been shown to inhibit the activation of pro-fibrotic factors by these cells when exposed to high glucose concentrations (Xu et al. 2018). The underlying mechanism for this effect was the attenuation of high glucose-induced upregulation of the transcriptional factor zinc finger E-box binding homeobox 1 or ZEB1 by Rg1 (Xue et al. 2018). Moreover, notoginsenoside R1, a component of *P notoginseng* was found to reduce the cytotoxic effect of high (30 mM) glucose concentrations administered to cultured rat retinal endothelial cells for up to 72 hours (Fan et al. 2017). This protection, which was associated with reduced apoptosis and decreased production of reactive oxygen species was attributed to improved intracellular redox state due to notoginsenoside R1 administration (Fan et al. 2017).

Diabetic nephropathy

Kidney disease represents a major component of sustained Type 1 and Type 2 DM which can manifest itself as severe damage and eventual kidney failure (Gnudi et al. 2016). The causes of diabetic nephropathy are complex but likely reflect capillary damage in the kidney glomeruli resulting in compromised filtration which deteriorates over time especially under poorly controlled diabetic conditions (Gnudi et al. 2016). There is substantial evidence suggesting that

ginseng and its related products can exert salutary effects in both Type 1 and Type 2 DM on diabetic nephropathy in experimental animals. In fact, both heat processed *P ginseng* (Kang et al. 2006, 2013) as well as *P quinquefolius* (Kim et al. 2007) have been shown to improve renal function in STZ-treated diabetic rats through a process likely involving a reduction in oxidative stress. Indeed, treatment with *P quinquefolius* reduced various markers of renal oxidative stress in STZ-treated diabetic rats, concomitant with improved metabolic status (Amin et al. 2011). Similar effects were seen with *P quinquefolius* administration to *ob/ob* and STZ-treated mice thus demonstrating efficacy in both Type 2 and Type 1 diabetic models, respectively (Sen et al. 2012). The protective effect of *P quinquefolius* was also attributed to both its hypoglycemic and antioxidant effects (Sen et al. 2012).

The beneficial effect of *P quinquefolius* was found to be mediated by ginsenoside Rg3 when administered to Otsuka Long-Evans Tokushima Fatty rats, a model of Type 2 DM (Kang et al. 2010). Interestingly, although unheated *P quinquefolius* also exerted beneficial effects these were generally less pronounced than those seen with the heat-processed variety (Kim et al. 2007; Yoo et al. 2012) which is likely related to increased levels of hypoglycemic saponin or other factors with heat processing (Jiao et al. 2014). Other studies as well have suggested that heated ginseng exerts superior benefit in reducing diabetic complications including renal dysfunction compared to the non-heated variety (Kim et al. 2007). Indeed, Korean ginseng appears to be particularly effective in this regard by substantially reducing renal damage as shown by preservation of glomerular structure and suppression of fibronectin production in STZ-treated rats (Quan et al. 2013). It was shown that these beneficial effects were likely due to inhibition of various proinflammatory factors including the cytokine TNF α whose synthesis is dependent on the transcriptional factor NF- κ B (Quan et al. 2013). It has been proposed that the beneficial

effect of Korean red ginseng is mediated by the presence ginsenoside Rg3 as well as maltol, whose contents are increased by heat processing (Kang et al. 2010). Administering *P notoginsenoside* to STZ-treated mice has also been shown to reduce renal damage possibly mediated by decreased renal VEGF expression and increased expression of bone morphogenetic protein-7, a member of TGF- β which plays a very important role in transforming mesenchymal cells into bone and cartilage (Tu et al. 2011a). Moreover, *P notoginseng* administration to alloxan diabetic rats produced a reduction in renal damage which was attributed to diminished levels of proinflammatory cytokines as well as activation of antioxidant proteins (Due et al. 2016). Renal protective effects have also been demonstrated with ginsenoside Rg3 when administered to STZ-treated diabetic rats, an effect associated with improved metabolic status (Kang et al. 2008). Protection against diabetic nephropathy, at least with respect to *P notoginsenoside* administered to STZ-induced diabetic rats was associated with decreased expression of the cytokine transforming growth factor β 1 (TGF- β 1) whereas the expression levels of Smad7, a nuclear protein and key regulator of TGF β activity was decreased (Tu et al. 2011b). Lastly, compound K was also recently shown to exert renal protective effect in STZ rats fed a high fat diet (Shao et al. 2015).

Erectile dysfunction

Erectile dysfunction is a condition associated with vascular abnormalities that also occurs in patients with chronic DM (Castela and Costa 2016). Administration of Korean ginseng extract to STZ-treated rats prevented erectile dysfunction which was attributed to an antioxidant effect (Ryu et al. 2005). Moreover, saponins extracted from *P notoginseng* had similar beneficial effects which were associated with reduced oxidative stress, apoptosis and improved endothelial function in the penile corpus cavernosum when administered to STZ-treated diabetic rats (Lin

and Gou 2013; Li et al. 2014b). A potentially important ginsenoside in this regard is Rg3 which reduced erectile dysfunction by reducing oxidative stress and neural degeneration when administered to STZ-treated rats for a three-month period (Liu et al. 2015).

Vascular integrity, vascularization and collateral blood vessel development

As a general underlying cause of many DM-related cardiovascular complications are vascular changes including the development of atherosclerosis, reduced vascular responsiveness to vasodilating factors as well as reduced ability to develop collateral vessels in response to injury. These have been addressed with respect to individual organ dysfunction, as discussed above although from a general perspective it should be emphasized that diabetes results in substantial vascular abnormalities which can be modulated by ginseng possibly *via* ginsenoside induced increase in nitric oxide production (Chen 1996). Excised femoral arteries, but not carotid arteries, from STZ-treated rats show a diminished endothelium-dependent vasodilating response to acetylcholine, an effect which was shown to be attenuated by treating the animals for 12 weeks with an aqueous extract of *P. quinquefolius* (Murias et al. 2018). There is substantial evidence that ginseng can positively or negatively modulate angiogenesis thus enhancing opportunity for new blood vessel development or to limit angiogenesis which would be of benefit for the treatment of cancers. With respect to enhancing angiogenesis, this appears also to be the case with respect to DM. For example, treatment of diabetic mice with ginsenoside Rg1 improved angiogenesis in the ischemic hindlimb which was proposed to occur *via* a number of mechanisms including increased eNOS activation, increased VEGF expression and inhibition of apoptosis (Yang et al. 2012).

A summary of some of the observed salutary effects of ginseng and ginseng-related products is shown in Table 2.

Clinical evidence of benefit

Although some studies have reported that ginseng administration has no effect on glucose levels or insulin sensitivity in non-diabetic individuals (Reay et al. 2009; Cho et al. 2013), others have shown increased postprandial insulin sensitivity following administration of ethanolic extracts of either Korean ginseng or *P. quinquefolius* (De Souza et al. 2015). There is also evidence of benefit by ginseng in patients with Type 2 DM. Although involving only a small sample size of only 36 diabetic patients, treatment for eight weeks with ginseng produced various beneficial effects including improved psychological status and reduced fasting blood glucose levels (Sotaniemi et al. 1995). In a small trial of 18 patients, a vinegar extract of *P. ginseng* produced moderate favourable effects on glucose homeostasis and glycemic control after eight weeks of treatment in patients with Type 2 DM (Yoon et al. 2012). There appears to be benefit as well in terms of reducing plasma indices of inflammation in Type 2 DM patients following twenty-four-week treatment with a combination of equal parts ginseng root, mulberry leaf and banaba leaf extract water extract for a period of 24 weeks (Kim et al. 2012). Low-grade inflammation was assessed by a number of plasma markers including levels of the vascular cell adhesion molecules VCAM-1 and ICAM-1 as well as oxidized low-density lipoprotein, thus the reduction in these factors suggests potential vascular protection by this treatment regimen. It is interesting that although both mulberry leaf and banaba leaf are also known to improve metabolic status in diabetic mice, surprisingly the combination of the three herbs failed to improve glucose homeostasis in Type 2 DM patients (Kim et al. 2012). The reason for this is not known with certainty but as the authors propose this may involve, among other possibilities, the consequences of herb-herb interaction although the effects of individual herbs were not determined in this study (Kim et al. 2012).

A number of studies have also shown that administration of a *P quinquefolius* extract produces a post-prandial reduction in blood glucose levels in human healthy subjects as well as those with Type 2 DM subjected to a glucose challenge although these studies involved a very small sample size as well (Vuksan et al. 2000a, 2000b). Moreover, in patients with Type 2 DM with concomitant hypertension, treatment with a *P quinquefolius* extract in addition to standard DM and hypertension medications has been shown to reduce blood pressure levels and arterial stiffness, possibly related to improved endothelial function (Mucalo et al. 2013). In a more recent study, administration of a *P quinquefolius* was further shown to reduce blood glucose levels as well as blood pressure when administered with standard diabetes medication in a small group of 24 Type 2 DM patients (Vuksan et al. 2018). Importantly, there appears to be no evidence of adverse effects of *P quinquefolius* administration for up to twelve weeks to Type 2 DM patients (Mucalo et al. 2014; Vuksan et al. 2018).

Several small studies in patients with Type 2 DM showed that twelve-week Korean ginseng administration resulted in good glycemic control and improved plasma glucose and insulin levels although both studies failed to show clinical efficacy as determined by glycated hemoglobin levels (Vuksan et al. 2008; Bang et al. 2014). In contrast, administration of Korean ginseng or ginsenoside Re failed to produce beneficial effects on either insulin sensitivity, beta cell function or metabolic parameters in a small group of fifteen obese or Type 2 DM subjects, suggested to be possibly due to poor bioavailability following oral administration (Reeds et al. 2011). Moreover, Korean white ginseng (*P ginseng*) failed to improve glycemic control after acute administration to Type 2 DM patients (Shishtar et al. 2014a). However, arterial stiffness, a marker of cardiovascular risk, was reduced in these patients suggesting cardiovascular benefit (Shishtar et al. 2014a). Fermentation of Korean ginseng is believed to increase both bioavailability and

bioactivity and indeed fermented Korean ginseng has been shown to reduce postprandial glucose levels and increase insulin levels in Type 2 DM patients following four-week treatment (Oh et al. 2014). A review of clinical trials using Korean ginseng for the treatment of DM failed to provide strong evidence for clinical benefit (Kim et al. 2011).

Potential benefit of ginseng for the treatment of diabetic retinopathy was also demonstrated in more than two hundred patients with this condition treated for twenty four weeks with Danshen administered in the form of Danshen Dripping Pill, a *Radix notoginseng* containing formulation also containing other bioactive compounds (Lian et al. 2015). These patients demonstrated substantial improvement as determined by fluorescence fundus angiography and fundoscopic examination parameters compared to placebo, however the specific component of Danshen which contributed to the benefit cannot be stated with certainty. Moreover, a recent meta-analysis of thirteen small scale clinical trials concluded that Danshen Dripping Pill likely offers beneficial effects in patients with diabetic retinopathy by improving vision and slowing progression of the disease (Huang et al. 2017). It should be pointed out that Danshen Dripping Pill is currently undergoing clinical evaluation in a Phase III study for the treatment of diabetic retinopathy which was estimated to be completed in December 2017. However, at time of writing no results of this study have been published. Other details of this study can be found at the following website, <https://clinicaltrials.gov/ct2/show/NCT02388984>.

Administration of ginseng-containing Shenmai to patients with coronary heart disease and DM revealed cardiovascular benefit including improved vascular endothelial function and improved left ventricular function thus suggesting a cardiovascular protective effect of this preparation (Zhang et al. 2008).

Limitations and future directions

As with many other cardiovascular conditions for which ginseng treatment has been espoused, a limitation in implementing ginseng as a therapeutic strategy for DM-induced cardiovascular disorders is the lack of large placebo-controlled clinical trials although these trials suggest that safety of ginseng is not a major concern (Vuksan et al. 2001, 2018; Yeh et al. 2003; Shishstar et al. 2014b; Mucalo et al. 2014). Nonetheless, as already alluded to, limited clinical evidence as well as experimental studies suggest the potential usefulness of ginseng in treating DM *per se*, as demonstrated by a recent meta analysis of clinical trials in Type 2 DM patients (Gui et al. 2016), and potentially reducing cardiovascular consequences in the absence of ginseng's hypoglycemic effect. Other factors as well must be resolved should ginseng or indeed other herbal medications reach acceptable clinical status including standardization of quality of the preparation as well as better identification of the factor or factors underlying the beneficial effects (Sievenpiper et al. 2004). The latter may be a daunting task in view of the plethora of compounds contained in ginseng potentially contributing to clinical efficacy with both polysaccharides as well as saponin ginsenosides as likely contributors. Because of the paucity of large well-controlled clinical trials and contradictory results obtained in such trials (Yuan et al. 2012), it is difficult to recommend the use of ginseng or indeed other herbal medications for the treatment of DM and its cardiovascular complications, at the present time despite the robust experimental data (Cefalu et al. 2008).

Another important aspect which is important to address is the potential interaction of ginseng with standard anti-diabetes medication particularly in terms of potential deleterious effects. This issue has not been extensively studied although in animal studies it was shown that co-administration of a Korean Red Ginseng extract with metformin to STZ-treated rats for five

weeks produced an additive hypoglycemic effect in the absence of any changes in the pharmacokinetic properties of metformin (Nam et al., 2018). As already alluded to, clinical evidence, albeit from small scale studies, appear to support the safety of ginseng when administered to diabetic patients (Mucalo et al. 2014; Vuksan et al. 2018) although long term studies to determine both the efficacy and safety profiles with chronic ginseng administration involving larger population sizes are very much needed to support this conclusion.

Draft

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Figure 1. Simplified diagram illustrating some factors potentially contributing to vascular and cardiac dysfunction in diabetes associated with increased insulin resistance and hyperglycemia. Adipocytes likely play a major role by releasing both deleterious adipokines such as leptin and reactive oxygen species (ROS) ultimately enhancing risk of stroke and myocardial infarction (MI). Hyperglycemia can result in increased ROS and decreased beneficial nitric oxide (NO) production thus resulting in damage to vascular endothelial (EC) and vascular smooth muscle cells (VSMC). Moreover, diabetic cardiomyopathy may materialize due to glucose-induced increased ROS production potentially resulting in heart failure.

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Table 1. Summary of major facts related to diabetes and cardiovascular disease

Worldwide occurrence > 400 million
Four-fold increase in occurrence since 1980
Much of the increase in diabetes attributed to increase in Type 2 diabetes
Risk of coronary heart disease and stroke increased between two- and four-fold with diabetes
Risk of heart failure increased between two- and five-fold with diabetes
Cardiovascular disease major cause of death in diabetic patients

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Table 2. Experimental evidence for beneficial effects of ginseng and ginseng-related products on diabetes-related cardiovascular complications

Complication	Experimental model	Treatment	Reference
Cardiomyopathy	STZ mice	<i>P. quinquefolius</i>	Sen et al. 2013b
			Sen et al. 2012
	<i>db/db</i> mice	<i>P. quinquefolius</i>	Sen et al. 2013b
			Sen et al. 2012
	STZ rats	Ginseng*	Tsai et al. 2014
		Ginsenoside Rh2	Lo et al. 2017
	HFD + STZ rats	Shengmai Powder + Danshen Decoction	Ni et al. 2011
Cardiac ischemic injury	STZ rats	Ginsenoside Rb1	Wu et al. 2011
Retinopathy	STZ mice	<i>P. quinquefolius</i>	Sen et al. 2013b
	<i>db/db</i> mice	<i>P. quinquefolius</i>	Sen et al. 2013b
	STZ rats	<i>P. notoginseng</i> + other herbs	Gao et al. 2013
	Goto-Kakizaki rats	<i>P. notoginseng</i> + other herbs	Gao et al. 2013
	STZ rats	Korean red ginseng	Yang et al. 2016
Nephropathy	STZ rats	Heat processed <i>P. ginseng</i>	Kang et al. 2006
			Kim et al. 2007
	STZ rats	Heat processed <i>P. quinquefolius</i>	Kim et al. 2007
	STZ rats	<i>P. quinquefolius</i>	Amin et al. 2011
	<i>ob/ob</i> mice	<i>P. quinquefolius</i>	Sen et al. 2012
	STZ mice	<i>P. quinquefolius</i>	Sen et al. 2012
	OLETF rats	Heat processed <i>P. quinquefolius</i>	Kang et al. 2010
	OLETF rats	Ginsenoside Rg3	Kang et al. 2010
	STZ rats	Korean red ginseng	Quan et al. 2013
	STZ mice	<i>P. notoginseng</i>	Tu et al. 2011a
	Alloxan rats	<i>P. notoginseng</i>	Du et al. 2016
	STZ rats	Ginsenoside Rg3	Kang et al. 2008
	STZ rats	<i>P. notoginsenoside</i>	Tu et al. 2011b
	HFD+STZ rats	Compound K	Shao et al. 2015
Erectile dysfunction	STZ rats	Korean red ginseng	Ryu et al. 2005
	STZ rats	<i>P. notoginseng</i>	Lin & Guo 2013
			Li et al. 2014b
	STZ rats	Ginsenoside Rg3	Liu et al. 2015
Hindlimb ischemia	STZ mice	Ginsenoside Rg1	Yang et al. 2012
Vascular dysfunction	STZ rats	<i>P. quinquefolius</i>	Murias et al. 2018

*Ginseng species not provided; HFD, high fat diet; OLETF, Otsuka Long-Evans Tokushima Fatty; STZ streptozotocin

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