Hypoglycemic Activity of *Panax ginseng* in Animal and Human Studies

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Despite significant achievements in treatment modalities and preventive measures, the prevalence of diabetes has risen exponentially in the last decade. For example, the United States has seen a dramatic 33% rise in diabetes coupled to increases in obesity and inappropriate lifestyle (Morkdad *et al.*, 2000; Sorensen, 2000). The value of current therapies is unequivocal, yet inadequate. While physicians advocate aggressive use of drugs to tighten glucose control, many patients are more inclined toward use of alternative therapies that include diet, food supplements and herbal medicine, even though there is a general lack of evidence for their safety and efficacy. Consequently, evidence-based medical and government regulators are calling for more randomized clinical studies to provide evidences of efficacy and safety.

Complementary/alternative therapies (CATs) are increasingly used by the general populations. Herbal medicine is among the most popular therapies and ginseng is one of the most popular herbal remedies, and a number of health claims are made of it (Astin, 1998; MacLennan*et al.*, 1996; Brevoort, 1998). Ginseng root extracts have long been used in traditional Chinese medicine to restore and enhance well-being. These adaptogenic effects are described as increasing the resistance against noxious or stressful influences without impairing physiological functions (Chong and Oberholzer, 1988).

We has selected the Korean ginseng for further investigation as potentially emerging alternative therapy for type 2 diabetes mellitus (T2DM). We tried to generate an evidence to support that Korean ginseng with a specific composition may be useful in improving hyperglycemia, reducing associated risk factors such as diabetic nephropathy, hyperlipidemia and hypertension, and ameliorating insulin resistance. An identification of the active ingredients in Korean ginseng was also performed. Before the therapeutic potential of Korean ginseng as a novel agent for treatment of diabetes can be fully realized, further controlled trials with larger sample sizes and of

longer duration are required.

Hypoglycemic Activity in Human Studies

Most of the claims made for ginseng are anecdotal, or based on cellular and molecular research, as well as animal studies, with lack of demonstrated effect in humans for any of the claimed therapeutic properties (Vogler *et al.*, 1999).

Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, diabetes and sexual function. These claims are mostly based on uncontrolled or non-randomized studies. Uncontrolled studies cannot differentiate between non-specific effects, such as the natural course of disease, and specific therapeutic effects. Therefore, randomized controlled trials (RCTs) are needed to determine the true efficacy of ginseng. The aim of this section is to summarize the current evidence from RCTs for the efficacy of ginseng.

Acute Studies

Using traditional Chinese medicine to establish starting points for ginseng dosing and timing applications, Vuksan and his associates evaluated the efficacy of American Ginseng (AG) on postprandial glucose level in a series of four acute studies. AG was administered at doses from 1 to 9 g and at times of administration from 0 to 120 min before an oral glucose challenge in people with and without T2DM (Vuksan *et al.*, 2000a; Vuksan *et al.*, 2000b; Vuksan *et al.*, 2000c; Vuksan *et al.*, 2001). Taken together, AG demonstrated a good acute safety profile. Neither group of subjects reported side effects, with the exception of insomnia reported by a diabetic patient after AG in his first study (Vuksan *et al.*, 2000a). The data also suggested that escalation of dose and time of administration offered no added benefit in people with diabetes. Doses of 3, 6, and 9 g and administration times of 120, 80, 40, and 0 min before a 25 g oral glucose challenge were equally as efficacious at lowering postprandial blood glucose from 1520% (Vuksan *et al.*, 2000b). These reductions were achieved without an effect on glycemia before the oral glucose challenge. Effects were also observed beyond the oral hypoglycemic medications in which 6 of 9 subjects remained constant in the first acute study and 7 of the 10 remained constant in the second study. Taken together, the data suggested the possibility for an adjunctive role of AG in lowering postprandial glycemia without the fear of precipitated preprandial hypoglycemia.

Recently, Vuksan group also investigated the effects of a different batch of AG on glycemia

following a 75 g oral glucose tolerance test to see whether postprandial glucose lowering effect of ginseng is reproducible using AG with a different ginsenoside profile. Interestingly one batch of AG was unable to reproduce the postprandial hypoglycemic effects they observed previously. Possible explanations for this discrepancy include marked decrements in total ginsenosides and the key ratios PPD:PPT, Rb_1:Rg_1, and Rb_2:Rc. These results suggest that the ginsenoside profile of AG might play a role in its hypoglycemic effects. The involvement of other components cannot, however, be precluded (Sievenpiper *et al.*, 2002)

Long-term Studies

Sotaniemi and co-workers (Sotaniemi *et al.*, 1995) assessed patients with newly diagnosed T2DM, who received either 100 mg or 200 mg ginseng daily. At the end of an 8-week treatment period, psychophysical performance, mood and vigor were significantly improved compared with baseline in both ginseng groups. HbA_{1c} was significantly reduced in patients who received 200 mg ginseng, while a reduction of the fasting blood glucose level was observed in both ginseng groups compared with baseline.

Armed with dosing and timing response data, Vuksan and his colleagues conducted a long-term study in people with T2DM (Vuksan *et al.*, 2000d). They hypothesized that the postprandial blood glucose lowering effects following 1 g of AG could be sustained safely in type 2 diabetics. This hypothesis was tested using a double blind, placebo-controlled crossover trial. Twenty-four type 2 diabetic subjects (HbA_{1C}=7.1± 0.1%; BMI=28±5 kg/m^2) were randomized to consume 1 g of a standardized AG extract or placebo before each meal three times daily for eight weeks. Seventeen of the 24 subjects who were having their diabetes treated pharmacologically were also maintained constant on their medications throughout. After the first treatment phase, all subjects were washed out for at least 4 weeks and then crossed over to receive the alternate treatment. Plasma HbA_{1c}, glucose, and insulin were measured as primary endpoints. Preliminary results from the study demonstrated that consumption of AG extract modestly but significantly reduced HbA_{1c} compared with placebo. As well, fasting blood glucose significantly decreased with eight weeks of AG treatment, while insulin increased nonsignificantly compared to placebo. They concluded that an AG extract added to the conventional treatment of diabetes significantly improved glycemic and blood pressure control beyond conventional treatment alone.

Hypoglycemic Activity in Animal Studies

Evidence From Other Groups

Growing evidence from in vitro and animal models indicates that ginseng might have a viable use in diabetes. North American (McGuffin, 1997; Oshima *et al.*, 1987; Martinez and Staba, 1984), Chinese (Martinez and Staba, 1984; Ohnishi *et al.*, 1996), Siberian, Sanchi, and Korean Red (steam treated *Panax ginseng* C.A. Meyer) (Ohnishi *et al.*, 1996) ginsengs have been shown to possess significant hypoglycemic action in rodent models. The same is true for some of their fractions: saponins (ginsensoides), peptidoglycans (panaxans for the panax species and eleutherans for *Eleutherococcus senticosus*), and the water (DPG-3-2) and methanol (EPG-3-2) extracted fractions of Chinese ginseng (Ng and Yeung, 1985).

Recently, Attele and colleagues evaluated antihyperglycemic and anti-obese effects of *Panax ginseng* berry extract and its major constituent, ginsenoside Re, in obese diabetic C57BL/6J *ob/ob* mice and their lean littermates (Attele *et al.*, 2002). Animals received daily intraperitoneal injections of extract for 12 days. On day 12, 150 mg/kg extracttreated *ob/ob* mice became normoglycemic (137±6.7 mg/dl) and had significantly improved glucose tolerance. Additional studies demonstrated that ginsenoside Re plays a significant role in antihyperglycemic action.

Evidence From Our Data

Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKA^{y} mice (*Arch Pharm Res* 24, 214-218, 2001)

Antidiabetic activities and mechanisms for white ginseng radix (Ginseng Radix Alba, GRA) and white ginseng rootlet (Ginseng Radix Palva, GRP) were compared in KKA^{y} mice. After four week oral administration, fasting blood glucose levels in GRA- and GRP-treated group were markedly reduced as compared to the control group (Diabetic control, 304±53 mg/dl; GRA treated group, 182±10; GRP treated group, 191±10; $p<0.01$). To elucidate the hypoglycemic mechanism(s) of ginseng radices, glucose absorption from small intestine, hepatic glucokinase and glucose-6-phosphatase activities, PPARg expression in adipose tissue were examined. The data obtained strongly implicate that GRA can improve the hyperglycemia in KKA^{y} mice possibly through blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase, and GRP through upregulation of adipocytic PPARγ protein expression as well as blockade of intestinal glucose absorption.

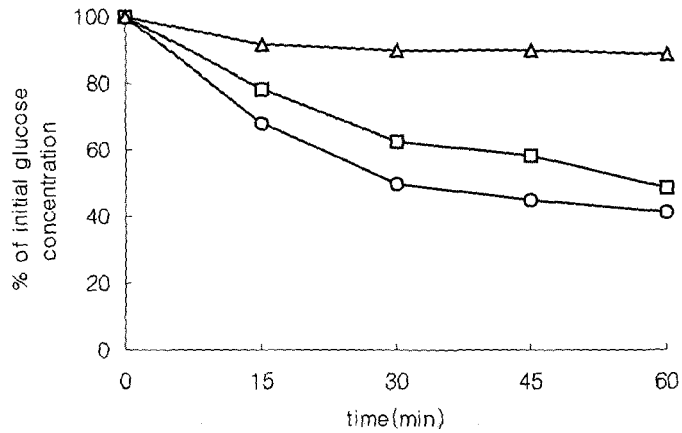

Fig. 1. Effect of the GRA on intestinal glucose absorption in SD rats. 10 mM glucose-Ringer solution without (○) or with 1 (□) or 5 mg/ml GRA (△) was circulated in small intestine of SD rats fasted for 16 h, and the glucose concentration in the circulation fluid was measured at the indicated times.

Incorporation of the glucose and insulin data into the HOMA (Homeostasis model assessment) model showed that GRA and GRP treatments improved insulin sensitivity by 89% and 78%, respectively. Significant improvements of insulin sensitivity in both groups are due to reduce plasma glucose levels as well as insulin levels.

Fig. 1 shows the effect of the GRA on the *in situ* intestinal absorption in normal SD rats. GRA showed the inhibitory effect on the glucose absorption in a concentration dependent manner. At 5 mg/ml concentration, GRA completely blocked the glucose absorption from the small intestine. This result is consistent to the findings of Onomura and his colleagues who demonstrated that ginseng radix inhibited sugar absorption in the small intestine possibly through blocking the actions of the Na^+/glucose cotransporter, SGLUT1 (Onomura *et al.*, 1999).

The thiazolidinediones, represented by rosiglitazone and pioglitazone, have recently been introduced as treatments of type 2 diabetics. These agents improve sensitivity to insulin by binding to the nuclear peroxisome proliferator activated receptor γ (PPARγ), which acts in conjunction with the retinoid X receptor by de-repression to increase transcription of certain insulin sensitive genes. In adipose tissue, where PPARg is most strongly expressed, stimulation by TZDs promotes the expression of genes encoding lipoprotein lipase (LPL), fatty acid transporter protein (FATP), adipocyte fatty acid binding protein (aP2), fatty acyl-CoA synthase, malic enzyme and the insulin-sensitive glucose transporter isoform GLUT4. Reduced PPARγ expression could have a dominant role in producing peripheral insulin resistance in type 2 diabetic

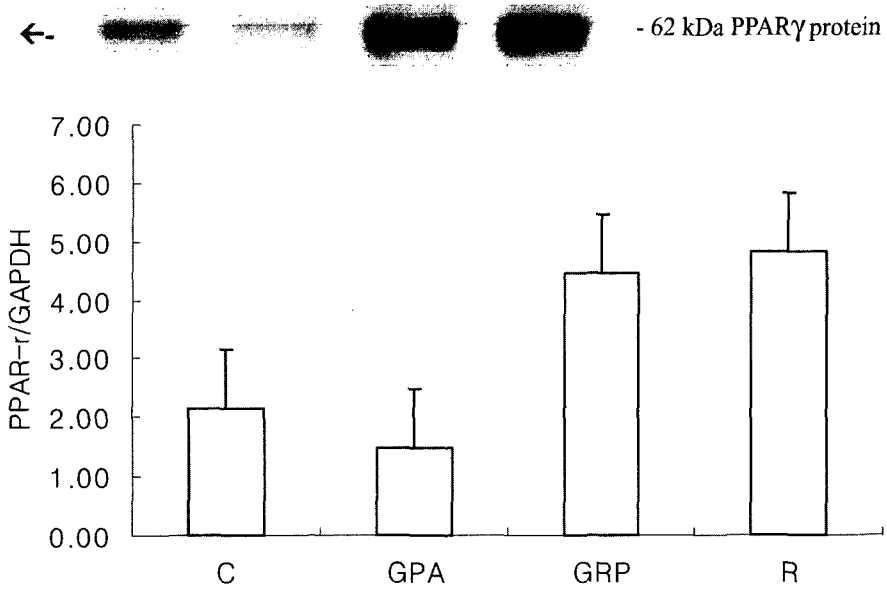

Fig. 2. Western blot analysis of PPARγ protein in epididymal fat from control, GRA, GRP and rosiglitazone (R) treated KKA^y mice. Epididymal fats were removed after 28 days of treatment without (C) or with drugs. 10 μg of proteins were separated by SDS-gel electrophoresis and western blotted.

patients. Fig. 2 shows the effects of GRA, GRP and rosiglitazone on expression of PPARγ protein in adipose tissue. Surprisingly, GRP-treated group revealed the adipocytic PPARg expression level comparable to group treated with rosiglitazone. In the meanwhile, GRA-treated group did not increased the PPARg protein expression.

Ginseng Radix Alba (GRA) prevents the onset of hyperglycemia as well as ameliorating developed hyperglycemia in multiple low dose streptozotocin-induced diabetic rats (Submitted)

In this study, we like to examine whether GRA exerts antidiabetic activities in both prevention and treatment modes in multiple low dose (MLD) streptozotocin (STZ) (20 mg/kg *i.p*) induced diabetic SD rats. In the prevention mode, 150 mg/kg of GRA water extract was administered intraperitoneally with STZ for 3 weeks, and this group is called CO150. In the treatment mode, we started to administer the same dose of GRA on day 8 and for another 3 weeks, and this group is called POST150. As shown in Fig. 3, GRA exerted significant hypoglycemic activities in both prevention (normal control, 97±6 mg/dl; diabetic control, 331±23; CO150, 211±37) and treatment groups (normal control, 128±4 mg/dl; diabetic control, 392±33; POST150, 263±44). Of great importance is the fact that plasma insulin levels in both groups were markedly increased as

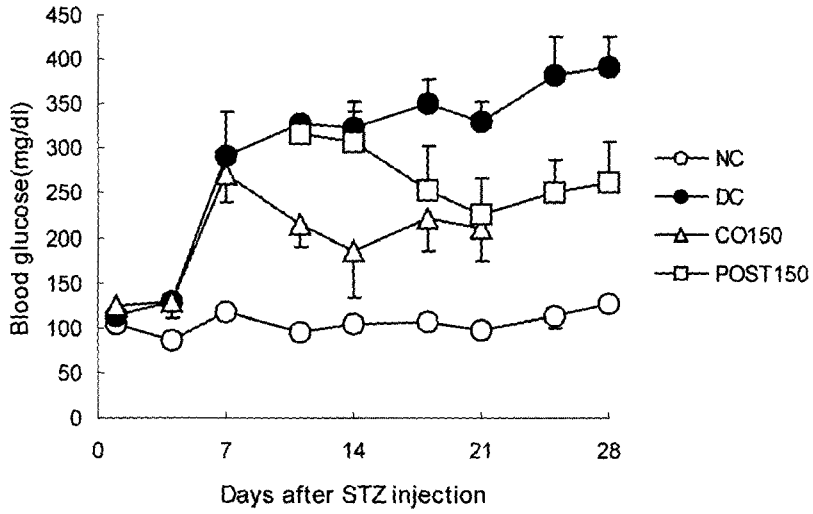

Fig. 3. Effects of co- or post-treatment of GRA water extract with streptozotocin on blood glucose levels. Data are mean±SE.

compared to the diabetic control (normal control, 428.7±62.1 pg/dl; diabetic control, 167.0±91.7; CO150, 377.6±68.7 in prevention mode, and in treatment mode normal control 417.9±84.6 pg/dl; diabetic control, 166.1±104.7; POST150, 315.2±47.4). Blood glucose levels were closely associated with plasma insulin levels, and this result may suggest that GRA showed the capacity to enhance insulin secretion as well as preventing destruction of pancreatic islet cells. Food and water intakes were also determined at the last week of treatment in both groups. Characteristic symptoms of diabetes were significantly improved in both groups. In the prevention mode, water intake (ml/rat/day) in normal control was increased from 30.6±1.5 to 122.2±3.4 in diabetic control rats. In the CO150-treated group, water intake was dramatically reduced to 68.3±4.4 ($p<0.001$ *vs.* diabetic control). In the treatment mode, POST-treated group also reduced the water intake from 128.9±2.2 to 113.3±1.7. Taken together, our data suggest that GRA water extract showed comparable antidiabetic activities in prevention and treatment modes. Therefore, GRA water extract may have a potential as a prophylactic as well as therapeutic agent for T2DM.

Hypoglycemic Mechanisms of *Panax ginseng*

Mechanisms underlying *Panax ginseng's* hypoglycemic action are not yet conclusive, but ani-

mal data so far support several possibilities that may work alone or together. There are three possibilities: (1) altered absorption and/or digestion of carbohydrate (Onumra *et al.*, 1999; Chung *et al.*, 2001), 2) improvement of insulin resistance (Oshima *et al.*, 1987; Yokozawa *et al.*, 1984; Hasegawa *et al.*, 1994; Attele *et al.*, 2002)), and (3) enhancement of insulin secretion (Kimura *et al.*, 1981; Hitonobu *et al.*, 1982). In our study, antidiabetic mechanisms of *Panax ginseng* water extract support the first two possibilities; oral administration of ginseng root water extract for 4 weeks to KKA^y mice improved the hyperglycemia through blocking intestinal glucose absorption as well as ameliorating insulin resistance by upregulation of adipocytic PPARg protein expression (Chung *et al.*, 2001). In the meantime, preliminary mechanistic trials that include acute insulin data on eight male and female nondiabetic subjects offer stronger support for post-absorptive effects, such as an enhancement of insulin secretion (Vuksan *et al.*, 1999). Vuksan and his associates observed that 6 g of American Ginseng (AG) administered 40 minutes before a 75 g oral glucose test increased postprandial insulin concentrations ~2-fold in the first 45 minutes following the challenge compared to the 75g-OGTT done alone previously. Also offering support to an insulin enhancing effect of AG is the nearly significant ($p = 0.084$). 25% increment in insulin action was observed in fasting insulin after eight weeks of AG supplementation in the long-term study.

Involvement of ginsenosides may play an important mechanistic role (Kimura *et al.*, 1981; Hitonobu *et al.*, 1982;; Yokozawa *et al.*, 1984; Hasegawa *et al.*, 1994; Onumra *et al.*, 1999). The ginsenoside Rb_1 was found to increase glucose uptake into sheep erythrocytes in a dose dependent manner (Hasegawa *et al.*, 1994). Another protopanaxadiol Rb_2 was also shown to increase the activity of the rate limiting glycolytic enzymes, glucokinase and phosphofructokinase, while decreasing the activity of the rate limiting gluconeogenic enzyme glucose-6-phophatase in rat liver preparations (Yokozawa *et al.*, 1984; Kimura *et al.*, 1981).

As mentioned earlier, Attele and his colleagues evaluated antihyperglycemic and anti-obese effects of *Panax ginseng* berry extract in *ob/ob* mice. Animals received daily intraperitoneal injections of *Panax ginseng* berry extract for 12 days. The improvement in blood glucose levels in the extract-treated *ob/ ob* mice was associated with a significant reduction in serum insulin levels in fed and fasting mice. A hyperinsulinemic-euglycemic clamp study revealed a more than twofold increase in the rate of insulin-stimulated glucose disposal in treated *ob/ ob* mice (112± 19.1 vs. 52±11.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ for the vehicle group, $P<0.01$). Improvement of insulin resistance in the *Panax ginseng* berry extract-treated *ob/ ob* mice was consistent with our results.

Other components alone or together with ginsenosides might also have antidiabetic activities. For example, the peptidoglycans (panaxans from asian ginseng and quinquefolans from AG) and polysaccharides (ginsenans) have shown pharmacological activities. Of these only the former have shown antihyperglycemic activity. Panaxans A-L (Konno *et al.*, 1984; Oshima *et al.*, 1985; Konno *et al.*, 1985) and quinquefolans A-C (Konno *et al.*, 1985) have shown hypoglycemic effects with varying potencies when administered as intraperitoneal injections in both normal and alloxan induced hyperglycemic mice. But their influence is dubious and hypoglycemic mechanism(s) are not known until now. Digestive gut and colonic microfloral enzymes would likely degrade these components and those that escaped digestion would be impermeable the enterocytes. There is, nevertheless, data that suggest that functional amounts of some intact peptides and peptidoglycans can be absorbed (Yamamoto, 2001).

Taken together, we may suggest that ginsenosides might be responsible for the improvements in glycemic control in our and other studies. However, evidences are still not enough to draw any conclusion. This is the reason why we are working on *Panax ginseng*.

Perspectives

Although there are many experimental evidences for antidiabetic action of *Panax ginseng*, we still need answers to the following questions in order to utilize *Panax ginseng* more rationally in clinical situations;

1) Does *Panax ginseng* really have a definitive antidiabetic efficacy comparable to conventional hypoglycemic drugs? Otherwise is *Panax ginseng* only a dietary supplement to conventional drugs? Is *Panax ginseng* safe enough to be used for long-term period?

2) Among saponin and non-saponin fractions of *Panax ginseng*, which fraction really represents hypoglycemic activity in type 2 diabetes? If saponin fraction is responsible for antidiabetic activity, which component(s) is a primary candidate? Identification and optimization of active components from *Panax ginseng* specific to diabetes will provide much interesting work for years to come.

3) Another interesting study is a "head-to-head" comparisons of various ginsengs, such as Korean ginseng (white and red), American ginseng, for antidiabetic activity to determine whether the effects observed with one species hold for other species. This work will shed light on potentially interesting chemical composition differences as they relate to specific physiological effects.

4) What is the hypoglycemic mechanism(s) of *Panax ginseng*? Do these mechanisms work alone or in concerted manner? Can we predict any adverse effects *Panax ginseng* may evoke acutely or chronically as far as hypoglycemic mechanisms are concerned? Are there any mechanisms related to anti-obesity activity of *Panax ginseng*?

References

Astin JA: Why patients use alternative medicine. Results of a national study. JAMA 279: 1548-1553 (1998)

Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, and Yuan CS. Antidiabetic Effects of *Panax ginseng* Berry Extract and the Identification of an Effective Component. *Diabetes* 51:1851-1858, (2002)

Brevoot P: The booming US botanical market a new overview. Herbalgram 44: 33-46 (1998)

Chong SKF, Oberholzer VG: Ginseng is there a use in clinical medicine? Postgrad Med J 64: 841-846 (1998)

Chung SH, Choi CG and Park SH: Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKA^{y} mice. Arch Pharm Res 24(3), 214-218 (2001)

Hasegawa H, Matsumiya S, Murakami C, Kurokawa T, Kasai R, Ishibashi S, Yamasaki K: Interactions of ginseng extract, ginseng separated fractions, and some triterpenoid saponins with glucose transporters in sheep erythrocytes. Planta Med 60: 153157 (1994).

Hitonobu IW, Masatoshi Y, Kimura M: Effects of hypoglycmic component of ginseng radix on insulin biosynthesis in normal and diabetic animals. J Pharm Dyn 5: 547554 (1982)

Kimura M, Waki I, Chujo T, Kikuchi T, Hiyama C, Yamazaki K, Tanaka O: Effects of hypoglycemic components in ginseng radix on blood insulin level in alloxan diabetic mice and one insulin release from perfused rat pancreas. J Pharm Dyn 4: 410417 (1981)

Konno C, Murakami M, Oshima Y, Hikino H. Isolation and hypoglycemic acvitity of panaxans Q, R, S, T and U glycans of Panax ginseng roots. J Ethnopharmacol ; 145(1): 69-74 (1985)

Konno C, Sugimyama K, Kano M, Hikino H. Isolation and hypoglycemic acvitity of panaxans A, B, C, D, and E glycans of Panax ginseng roots. Planta Med; 50: 434-436 (1984)

Martinez B, Staba EJ: The physiological effects of Aralia, Panax and Eleuthercoccus on exercised rats. Jpn J Pharmacol 35: 79-85 (1984)

McGuffin M: American Herbal Products Associations "Botanical Safety Handbook." Boca

Raton, FL: CRC Press (1997)

MacLennan AH, Wilson DH, Taylor AW: Prevalence and cost of alternative medicine in Australia. Lancet 347: 569-573 (1996)

Morkdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the US: 1990-1998. Diabetes Care 23: 1278-1283 (2000)

Ng TB, Yeung HW: Hypoglycemic constituents of Panax ginseng. Gen Pharmacol 16: 549-552 (1985)

Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E, Yano H, Tanigawa K, Seino Y: Effect of ginseng radix on GLUT2 protein content in mouse liver in normal and epinephrine-induced hyperglycemic mice. Biol Pharm Bull 19: 1238-1240 (1996)

Onumra M, Tsukada H, Fukuda K, Hosokawa H, Nakamura H, Kodama M, Ohya M, Seino Y: Effects of ginseng radix on sugar absorption in the small intestine. Am J Chin Med XXVII: 347354 (1999)

Oshima Y, Konno C, Hikino H: Isolation and hypoglycemic activity of panaxans I, J, K and L glycans of Panax quinquefolium roots. J Ethnopharmacol ;14:255-259 (1985)

Oshima Y, Sato K, Hikino H: Isolation and hypoglycemic activity of quinquefolans A, B, and C, glycans of Panax quinquefolium roots. J Nat Prod 50: 188190 (1987)

Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V: Variable effects of American Ginseng: A batch of American ginseng with a depressed ginsenoside profile does not affect p[ostprandial glycemia. Eur J Clin Nutr (in press)

Sorensen TI. The changing of lifestyle of the world. Diabetes Care 23(Suppl 2):B1-B24 (2000)

Sotaniemi EA, Haapakoski E, Rautio A: Ginseng therapy in non-insulin-dependent diabetic patients. Diabetes Care 18: 1373-1375 (1995)

Vogler BK, Pittler MH, Ernst E: The efficacy of ginseng: a systematic review of randomized clinical trials. Eur J Clin Pharmacol 55: 567-575 (1999)

Vuksan V, Sievenpiper JL, Koo VYY, Beljan U, Xu Z: American ginseng (Panax Quinquefolius L.) reduces postprandial glycemia when taken prior to the test meal. Proceedings of the 17th International symposium of Diabetes and Nutrition, p. 12, A17, Versailles, France, July 1999.

Vuksan V, Sievenpiper JL, Koo VYY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E: American ginseng reduces postprandial glycemia in nondiabetic and diabetic individuals. Arch Intern Med 160: 1009-1013 (2000a)

Vuksan V, Stavro MP, Sievenpiper JL, Koo VY, Wong E, Beljan-Zdravkovic U, Francis T, Jenkins AL, Leiter LA, Josse RG, Xu Z.: American ginseng improves glycemia in individuals with normal glucose tolerance: effect of dose and time escalation. J Am Coll Nutr 19(6):738-44 (2000b)

Vuksan V, Leiter AL, Stavro MP, Josse RG, Sievenpiper JL, Xu Z, Beljan-Zdravkovic U: Similar postprandial glycemic reductions with escalation of dose and administration time of American Ginseng type 2 diabetes. Diabetes Care 23: 1221-1226 (2000c)

Vuksan V, Xu Z, Jenkins AL, Beljan-Zdravkovic U, Sievenpiper JL, Leiter LA, Josse RG, Stavro MP: American Ginseng improves long term glycemic control in Type 2 diabetes: Double-blind placebo controlled crossover trial. American Diabetes Association Annual Meeting, Diabetes Suppl (1) A95, Abstract No. 384 (2000d)

Vuksan V, Sievenpiper JL, Wong J, Xu Z, Beljan-Zdravkovic U, Arnason JT, Assinewe V, Stavro MP, Jenkins AL, Leiter LA, Francis T.:American ginseng (Panax quinquefolius L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals. Am J Clin Nutr Apr; 73(4): 753-8 (2001)

Yamamoto A. Improvement of transmucosal absorption of biologically active peptide drugs. Yakugaku Zasshi 121, 929-948 (2001)

Yokozawa T, Kobayashi T, Kawai A, Oura H, Kawashima Y: Stimulation of lipid and sugar metabolism in ginsenoside-Rb2 treated rats. Chem Pharm Bull 32: 27662772 (1984)