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Effect of American ginseng (*Panax quinquefolius* L.) on arterial stiffness in subjects with type-2 diabetes and concomitant hypertension

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ABSTRACT

Ethnopharmacological relevance: Substantial pre-clinical and some clinical data are available showing that Asian ginseng (*Panax ginseng* C.A. Meyer) varieties or its particular ginsenosides exert a vasodilatating effect, thus may modulate vascular function. However, the clinical evidence for American ginseng (*Panax quinquefolius* L.) is scarce. Therefore, this study evaluates the effect of American ginseng (AG) on arterial stiffness, as measured by augmentation index (AI), and blood pressure (BP), in type 2 diabetes patients with concomitant hypertension.

Materials and methods: Using a double-blind, placebo-controlled, parallel design, each participant was randomized to either the selected AG extract or placebo at daily dose of 3 g for 12 weeks as an adjunct to their usual antihypertensive and anti-diabetic therapy (diet and/or medications). AI and BP were measured by applanation tonometry at baseline and after 12 weeks of treatment.

Results: A total of 64 individuals with well-controlled essential hypertension and type 2 diabetes (gender: 22 M:42 F, age:63 ± 9.3 years, BP: 145 ± 10.8/84 ± 8.0 mmHg, HbA1c: 7.0 ± 1.3%, fasting blood glucose (FBG): 8.1 ± 2.3 mmol/L) completed the study. Compared to placebo, 3 g of AG significantly lowered radial AI by 5.3% ($P=0.041$) and systolic BP by 11.7% ($P<0.001$) at 12 weeks. No effect was observed with diastolic BP.

Conclusions: Addition of AG extract to conventional therapy in diabetes with concomitant hypertension improved arterial stiffness and attenuated systolic BP, thus warrants further investigation on long-term endothelial parameters before recommended as an adjunct treatment.

1. Introduction

Complementary and alternative medicine (CAM) use has increased at a considerable pace in recent years (Barnes et al., 2008). Among U.S. adults, almost four out of 10 reported using CAM therapy, with ginseng being the fifth most commonly used herbal product (Barnes et al., 2008). The two major species of ginseng that have been well documented in traditional pharmacopoeias and used as therapeutic agents are *Panax quinquefolius* L. and *Panax ginseng* C.A. Meyer, commonly referred to as American ginseng and Asian ginseng (Jia and Zhao, 2009). American ginseng (AG) is mainly grown in North America (Jia and Zhao, 2009) with Ontario, Canada being one of the largest producers. To date, various ginsenosides, considered as the major active constituents of ginseng, have demonstrated mainly in preclinical studies a potential benefit on vascular endothelial function, specifically due to endothelium-dependent release of nitric-oxide (NO) (Chen, 1996; Kang et al., 1995; Kim et al., 1992; Yuan et al., 1999). Accumulating clinical evidence concerning the potential benefits of ginseng roots in vascular pathology imply that ginseng species might improve endothelial dysfunction and arterial stiffness in healthy individuals (Jovanovski et al., 2010) and patients with hypertension and type 2 diabetes by increasing NO bioavailability and preventing

Abbreviations: AG, American ginseng; AI, augmentation index; BP, blood pressure; CAM, complementary and alternative medicine; NO, nitric-oxide; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; IQOLA SF-36v2, international quality of life assessment SF-36 Version 2.0; PPD, protopanaxadiol; PPT, protopanaxatriol; BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; KRG, Korean red ginseng; baPWV, brachial-ankle pulse wave velocity

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free radical injury to the vascular endothelium (Han et al., 2005; Lee and Son, 2011; Xu et al., 2000). Arterial stiffness is increasingly recognized as an important determinant of cardiovascular disease (CVD) risks (Mitchell et al., 2012), and has demonstrated independent predictive value in various patient groups (London et al., 2001; Safar et al., 2002; Weber et al., 2005; Williams et al., 2006). Individuals with diabetes are at particularly high risk of CVD events due to the multifaceted ethiology of disease and associated abnormalities in both micro and macrovascular structure and function. Augmentation index (AI), one of several non-invasive methods used to assess arterial stiffness, provides additional insight concerning arterial wave reflections during a cardiac cycle (Laurent et al., 2006), thus rendering information on hemodynamic potential of compounds such as AG. Aside from hemodynamic potential of cited ginseng species, the whole root of AG generated a neutral effect on blood pressure both acutely and long-term in individuals with hypertension (Stavro et al., 2005, 2006). However, there are substantial compositional alterations in phytochemical composition, including ginsenoside profiles, following ethanol extraction methodologies typically used in production of marketed AG preparations; hence, the physiological effects of extracted AG remain unknown.

In light of insufficiency of convincing clinical data demonstrating namely AG's effect on arterial hemodynamics, there is a need for well-designed, randomized clinical trials. This study therefore explores the effect of AG extract on arterial stiffness and blood pressure in individuals with type 2 diabetes and concomitant hypertension. To the best of our knowledge, this is the first randomized, placebo-controlled, double-blind study evaluating the long term effect of AG root extract on arterial hemodynamics via pulse wave analysis.

2. Materials and methods

2.1. Participants

Sixty four individuals (30 intervention and 34 placebo) with essential hypertension were recruited from the diabetes outpatient clinic. All patients had well-controlled type 2 diabetes for >6 months without manifest complications and were metabolically stable (average HbA1c: $7.0 \pm 1.3\%$ and average FPG: 8.1 ± 2.3 mmol/L) on diet and/or conventional diabetes therapies. In addition to diagnosed type 2 diabetes, eligibility criteria included: age over 40 years and the use of antihypertensive medications for >6 months prior to the commencement of the study. Exclusion criteria included systolic BP >160 mm Hg or diastolic BP >100 mm Hg, secondary hypertension, pregnancy, kidney or liver disease, unstable angina, use of ginseng within 2 months prior to the initiation of the study, and a weight fluctuation of ± 2 kg during the treatment periods. All subjects gave informed written consent before taking part in the study, approved by the institutional ethics board. Research followed guidelines of the Declaration of Helsinki and Tokyo.

2.2. Treatments

Participants were randomly assigned to one of the two interventions and received, prior to each of the main meals, three times daily two 500 mg capsules (total 3 g/day), of either American ginseng extract or identical-appearing placebo capsules containing corn starch. The AG intervention was prepared using a proprietary ethanol extraction containing 10% total ginsenosides. The dose has been selected based on data from the long-term study derived from the acute-to-chronic clinical testing program for AG (Vuksan and Sievenpiper, 2005). Furthermore, a dose of 3 g is in alignment with the 1–3 g dose recommended by the Commission E monograph and WHO ginseng monograph (Blumenthal, 1998; World Health Organization, 1999). Both interventions were taken simultaneously with usual antihypertensive and hypoglycaemic medications, which included maintenance of the type and dose of such therapies in addition to adherence to dietary recommendations. Randomization to intervention was done using a computer-generated random number table. Subjects, investigators and statistician were blinded to the identity of the placebo and ginseng capsules by coding and by the indiscernible nature of the capsules.

2.3. Protocol

The study used a randomized, placebo-controlled, double-blind design. Presented data represents a secondary subset analysis of trial data evaluating AG in diabetes control as a primary outcome measure (unpublished to date). The first study phase was a recruitment phase during which interested patients were invited to the clinic to attend an information session providing details about the study procedure. Prospective patients were invited back to the clinic after a 10–12 h overnight fast for screening that included a blood sample and completion of medical questionnaires. Patients who satisfied the inclusion criteria proceeded to the second phase were they were randomized to either the AG or placebo arm for the 12-week follow up period. Throughout the intervention phase, patients attended the clinic every 6 weeks (weeks 0, 6 and 12) to have biochemical and anthropometric measurements taken, complete IQOLA SF-36v2 questionnaire (Ware and Sherbourne, 1992), receive a new treatment batch, return unused pills, and conduct an interview with the dietician. At the baseline and following 12 weeks of intervention, vascular assessment was performed. Patients were advised to maintain initial body weight, and follow consistent dietary and physical activity patterns throughout the study. They were also asked to refrain from all medications including AG or placebo during the preceding 12 h prior to the study visit.

Brachial BP was assessed on the dominant arm with an automatic oscillometric device (HEM-9000AI; Omron Healthcare, Kyoto, Japan) according to standard procedure (Chobanian et al., 2003). Prior to measurements, the patients remained seated in a quiet, temperature-controlled room for 5 min with arm supported at heart level to achieve resting heart rate and blood pressure. Subsequently, three one-minute-apart readings were obtained from the brachial artery, and meaned. Thereafter, patients underwent a non-invasive measurement of arterial stiffness using applanation tonometry (HEM-9000AI; Omron Healthcare) at weeks 0 and 12 of the treatment. Pressure sensor was positioned at radial artery for each AI measurement, obtaining continuous steady-state recordings over a period of 30 s; three measurements were taken at each visit, and the mean AI was used for analysis. Primary vascular endpoint included AI as a measure of arterial hemodynamics, whereas secondary clinical endpoints included BP, heart rate and pulse pressure.

2.4. Ginseng analyses

American ginseng root was supplied by the Ontario Ginseng Growers (Simco, ON, Canada), combining five batches from five major farms (ratio 1:1:1:1:1) to be representative of entire growing area. The ginsenoside extract was produced by repeated extraction using 70% food-grade ethanol. Analyses of six common ginsenosides were determined by high-performance liquid chromatography/mass spectrometry by duplicate injection for characterization purposes (Hwelett-Packard 1100 HPLC with DAD detector). Total ginsenoside concentrations (%w/w) were 4.092. Individual concentrations for the protopanaxadiol (PPD) ginsenosides Rb1, Rc, Rb2, and Rd were 2.558%, 0.18%, 0.032%, and 0.402%, respectively, and for the protopanaxatriol (PPT) ginsenosides Rg1 and Re were 0.086% and 0.834%, respectively. The PPD:PPT ratio was 3.45.

An individual otherwise not involved in the study performed the weighing, encapsulation, and blinding of treatments. Both treatments were individually encapsulated and coded in identical size 500 mg opaque capsules.

2.5. Data analyses

Per-protocol analyses were conducted. Change in radial AI, the primary vascular outcome measure, was calculated at baseline and after 12 weeks for each intervention. A sample size of 30 subjects per group was calculated (80% power, $\alpha=0.05$) as efficient to demonstrate a change by 4% (SD=8) in AI. The demographic findings and participant characteristics where compared using a *t*-test for independent samples and λ^2 test for the intervention and control groups. Comparison between groups and treatment end differences in BP and AI were assessed using Factorial ANOVA and Fisher LSD test. Results were expressed as number of participants (n), mean $\pm$ SD, range (minimum–maximum), and significant at $P<0.05$. Statistical analyses were performed using STATISTICA v 6.1 (StatSoft Inc., USA).

3. Results

Eighty-one participants were assessed for their eligibility and enrolled in the study. Study flow is presented in Fig. 1. Dropouts on AG and placebo arms were 10 and seven, respectively. Reasons for dropouts during the protocol included unstable hypertension control at commencement of the study ($n=10$), change in medication therapy ($n=5$) and inability to continue ($n=2$). Medication change refers to any change in type or dosage of the antihypertensive and/or antihyperglycemic therapy the patients were receiving. Unstable hypertension control refers to a systolic BP > 160 mmHg and diastolic BP > 100 mmHg measured at the commencement of the study (week 0), following screening. Two patients declined to continue for the following reasons; one was hospitalized due to glaucoma, and the other stated lack of time for completion of the study.

Sixty-four participants (22 men and 42 women), aged 63 ± 9 years (mean $\pm$ SD), with essential hypertension and type 2 diabetes, who met the eligibility criteria, completed the study. They followed the study protocol without difficulty and reported no side effects after consumption of either AG or placebo. Analysis of baseline parameters revealed that the two groups were similar in all demographic and clinical parameters ($P>0.05$). However, baseline body mass index (BMI) was significantly higher in the group randomized to ginseng arm, and waist-to-hip ratio (WHR) in the control treatment arm (Table 1). Within- and between-treatment differences in markers of compliance were assessed for AG and placebo. Body weight change from week 0 to week 12 (0.13 ± 2.86 kg vs. -0.50 ± 3.04 kg) was not significantly different between AG and placebo. The proportion of pills consumed over the 12 weeks was above 80%, and it did not differ between the two groups.

Within- and between-treatment differences were assessed for AG and placebo in AI and BP. There was a significant dependent and independent effect of treatment and time on AI changes. Moreover, a significant reduction in AI following AG extract intervention was observed at 12 weeks compared to placebo ($P=0.041$) (Table 2). Systolic BP (SBP) was significantly improved during AG compared with placebo ($P<0.001$). AI decreased by 5.25% and SBP by 11.72% on AG compared with placebo after 12 weeks of treatment. No significant between-treatment end difference in diastolic BP (DBP) was observed. A significant within-treatment decrease during AG was found in both SBP ($P<0.001$) and DBP ($P=0.002$), and in DBP during placebo intervention ($P=0.003$) (Table 2).

The mean absolute AI, BP, heart rate and pulse pressure values did not differ significantly between both interventions at baseline. There was no effect of study period on AI, SBP, or DBP Table 3.

4. Discussion

To the best of our knowledge, the present study is the first randomized controlled trial to examine the effect of AG on pulse wave reflection, as measured by AI. We found that the consumption of AG extract significantly improved arterial stiffness compared to a control in individuals with type 2 diabetes and concomitant hypertension following 3 month supplementation.

Recent clinical data confirm the value of arterial stiffness as an independent predictor of CV events (Laurent et al., 2006). A generally accepted mechanistic view is that an increase in arterial stiffness and

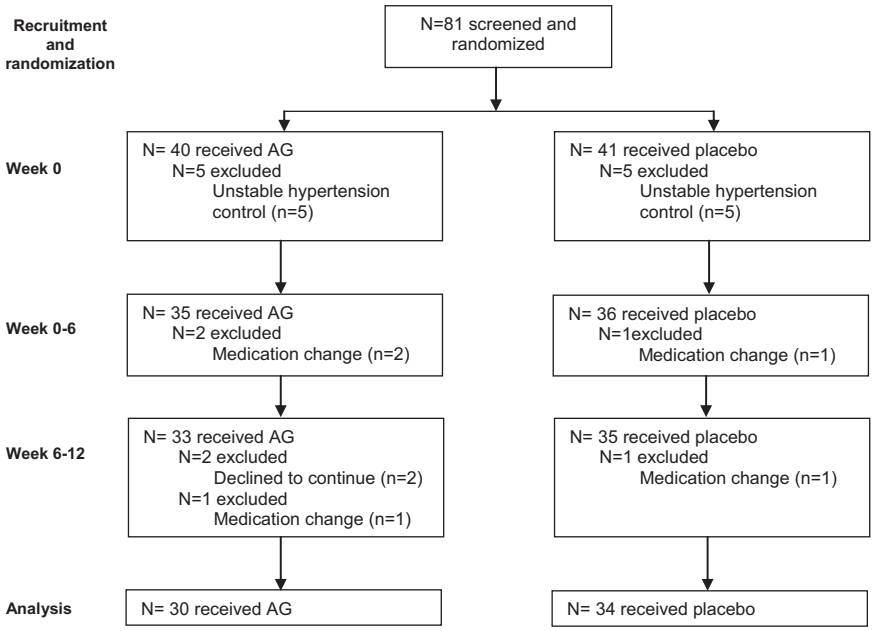

Fig. 1. Schematic of the flow of participants through the trial exploring the effect of AG treatment on arterial stiffness in hypertensive and type 2 diabetic patients.

Table 1
Baseline characteristics of study subjects.

Variables	Group		P
	Intervention	Control	
Sample size (n)	30	34	
Gender male/female	10/20	12/22	0.869
Age (years)	62.1 ± 8.80	63.9 ± 10.93	0.282
Weight (kg)	88.5 ± 16.09	80.8 ± 16.43	0.066
BMI (kg/m^2)	33.4 ± 5.60	29.9 ± 4.95	0.012
WHR (%)	94.4 ± 5.87	100.3 ± 3.69	0.003
HbA1c (%)	7.2 ± 1.34	6.9 ± 1.28	0.450
FPG (mmol/L)	8.6 ± 2.61	7.5 ± 1.89	0.057
Antihypertensive agents	30	34	0.988
Number taking 1 agent/ ≥ 2 agents	16/14	17/17	
Number taking specific agents	BB(8), CCB(7), ACE(15), ARB(0), D(1), α-B(1), mox(2), fixed comb. (16)[a]	BB(5), CCB(8), ACE(23), ARB(1), D(3), α-B(1), mox(2), fixed comb. (14)[a]	
Oral hypoglycemic agents	30	26	0.326
Number taking 1 agent/ ≥ 2 agents	9/21	16/10	
Number taking specific agents	MET(22), SULPH(23), DPP-4(5), GLP-1(1), MET+TZL(1), ACA(2)	MET(20), SULPH(12), DPP-4(5), GLP-1(0), MET+TZL(0), ACA(0)	
Hypolipemic agents	23	29	0.785
Number taking 1 agent/ ≥ 2 agents	20/3	27/2	

Data expressed as mean ± SD.
BMI, body mass index; WHR, waist-to-hip ratio; HbA1c, glycated hemoglobin; and FPG, fasting plasma glucose.
ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; D, diuretic; α-B, alpha-blocker; mox, moxonidin (central alpha adrenergic agonist); and fixed comb., fixed-dose combination antihypertensives.
P-value by the independent *t*-test or the Yates corrected Chi-square test, as appropriate.
[a] ACE+D; ARB+D; and ACE+CCB.

Table 2
Change in AI, systolic BP, diastolic BP, pulse pressure and heart rate within control and AG intervention groups.

Parameter	Control group (34)		Δ (%)	Intervention group (30)		Δ (%)
	Week 0	Week 12		Week 0	Week 12	
AI (%)	89.5 ± 13.80	86.9 ± 9.22	2.59 (2.89)	85.2 ± 12.53	80.7 ± 12.36	4.47 (5.25)
Systolic BP (mmHg)	142.6 ± 11.15	143.2 ± 16.23	−0.64 (−0.45)	148.5 ± 9.65	131.1 ± 13.13	17.40 (11.72)
Diastolic BP (mmHg)	84.6 ± 6.99	78.3 ± 8.09	6.32 (7.47)	84.9 ± 9.19	77.8 ± 10.05	7.16 (8.43)
Pulse pressure (mmHg)	64.8 ± 17.59	64.1 ± 12.61	0.70 (1.08)	62.5 ± 13.27	56.1 ± 12.43	6.42 (10.27)
Heart rate (beats/min)	76.7 ± 10.33	76.8 ± 9.60	−0.08 (−0.10)	80.9 ± 12.99	81.8 ± 13.11	−0.84 (−1.04)

Data expressed as mean ± SD.

Table 3
Between and within-treatment change-from-baseline differences in AI, systolic BP, diastolic BP, pulse pressure and heart rate.

Parameter	Control group week 0 vs. week 12[a]	Intervention group week 0 vs. week 12[a]	Week 0 control group vs. intervention group[a]	Week 12 control group vs. intervention group[a]
AI	0.378	0.154	0.152	*0.041*[c]
Systolic BP	0.863	*< 0.001*[b]	0.068	*< 0.001*[c]
Diastolic BP	*0.003*[d]	*0.002*[b]	0.865	0.821
Pulse pressure	0.110	0.066	0.689	*0.018*[c]
Heart rate	0.974	0.780	0.145	0.087

[a] Fisher LSD.
[b] Both systolic and diastolic BP have decreased significantly in the intervention group after 12 weeks of intervention.
[c] A significant reduction in AI ($P = 0.041$), systolic BP ($P < 0.001$) and pulse pressure ($P = 0.018$) was observed following AG extract intervention at 12 weeks compared to placebo.
[d] A significant within-treatment decrease was found in {C}{C}{cke_protected_1}-{C}{C}{cke_protected_2}DBP during placebointervention ($P = 0.003$).

peripheral resistance causes a premature and amplified return of reflected waves in late systole, decreasing ventricular perfusion while increasing systolic BP (Laurent et al., 2006). In this regard, clinical trials show that antihypertensive agents, such as CCBs and ACE-inhibitors have additional beneficial influence on central AI beyond blood pressure (Williams et al., 2006), possibly by decreasing peripheral resistance (Ting et al., 1995; Taddei et al., 2001; Hornig et al., 2001). Therefore, additional focus should be placed on pharmacological treatments that are able to reduce arterial stiffness including antihypertensive and antihyperglycemic agents (Kool et al., 1995; Nakamura et al., 2004; Ting et al., 1995).

The potential benefit of ginseng on vascular function has been suggested by a number of investigators. It has been found that ginseng extract exerts a direct vasodilatory effect on isolated blood vessels that may be due to endothelium-dependent release of nitric oxide (NO) (Kim et al., 1992). Arterial stiffness and endothelial dysfunction have been clinically linked to decreased NO generation and increased NO inactivation (De Vriese et al., 2000; Ungvari et al., 2010). Therefore, improvement of vascular endothelial function through the NO pathway by treatment with AG could be one of the proposed mechanisms responsible for decreased arterial stiffness. In fact, a correlation of NO generation and improved glycemic control in patients with diabetes was previously reported during AG treatment (Xu et al., 2000). By assessing arterial wave reflection, additional information on ginseng's potential role in improving vascular function could be obtained in this patient population.

Previous studies using steamed *Panax ginseng* spp., provided inconsistent results regarding ginseng's impact on pulse wave reflection. A study that investigated the acute effect of Korean red ginseng (KRG) root on AI found a significant amelioration of pulse wave reflection (Jovanovski et al., 2010). Conversely, two previous 3-month studies found that oral administration of KRG did not significantly affect arterial stiffness, as measured by brachial-ankle pulse wave velocity (baPWV) (Park et al., 2012; Rhee et al., 2011). However, different ginseng spp. (AG vs. KRG), study population and measurement methods of arterial stiffness render it difficult to make direct comparisons.

A decrease in peripheral SBP by AG treatment was observed as expected, with respect to AI decrease. This finding suggests that an earlier return of the wave reflection from the periphery, a distinctive feature of stiffer arteries in hypertension, is associated with an increase in systolic BP. Therefore, the observed changes in AI may have occurred dependent of their effects on systolic BP.

Former research evaluating the potential of whole root AG as a vasodilatatory agent, showed either beneficial (Stavro et al., 2000; Xu et al., 2000) or neutral effects (Stavro et al., 2005; Stavro et al., 2006) on BP in subjects with hypertension or type 2 diabetes. AG ethanol extract used in our study was different from those previously used which may have had a different ginsenoside profile and higher total ginsenosides present. The ethanol extract studied here was concentrated to have 10% total ginsenosides which is considerably higher (i.e. up to 65%) than the quantity delivered in the previous trials mentioned. The extraction also modifies the proportion of individual ginsenosides relative to the ratios present in the native root. For example, the ratios of Rb1 and Re and Rd ginsenosides, that may have vasomodulatory potential, have been proportionally increased compared to the fractions found in the main root. Due to the compositional differences present among materials studied the results seen with one ginseng species might not apply to other or even the same species, especially if administered as a raw root vs. an extract. In an attempt to quantify the extent of variability in the active components found in ginseng, an analysis of the coefficient-of-variation in ginsenosides across ginseng type, assay-technique, and ginsenoside-type was previously undertaken (Sievenpiper et al., 2004; Vuksan and Sievenpiper, 2005) demonstrating that the ginsenoside composition is highly variable across different ginseng source parameters.

Second, we had a group of individuals with both hypertension and type 2 diabetes. Therefore, to better understand the influence of a dose-effect relationship on patients with both comorbidities, further research is warranted.

Despite significant effects on systolic blood pressure, there was no change in diastolic pressure across intervention groups. In older individuals with concomitant CVD risk hypertension is characterized by high systolic BP and high PP (Franklin et al., 1997). Higher SBP, left untreated, may accelerate large artery stiffness and thus perpetuate a vicious cycle (Franklin et al., 1997). These characteristics were consistent in our sample cohort with the mean age of 63 years. Therefore, it is expected that the greatest pressure shift was noticed in systolic BP, confirmed by the AI data.

The current study was limited in several ways. First, although antihypertensives were instructed not to be taken on the test mornings, they were taken at least 12–24 h beforehand, and could have thus residually affected BP. Nonetheless, participants were thoroughly instructed to maintain the type, dose and timing of their antihypertensives constant, which was not different between two groups. Finally, the results may not be generalizable to other sources of AG or any other ginseng extracts. High variability in ginsenosides which has been detected in various ginseng sources and different extraction methods (Sievenpiper et al., 2004) may result in just as high of a variability in efficacy and potentially in safety across batches. Furthermore, additional insights into potential vasoactive differences between root and extract should be undertaken. In the absence of efficacy based standardization, the use of ginseng in improving vascular parameters must be approached cautiously. Nevertheless, an AG with a matched PPD:PPT ginsenoside ratio may show similar efficacy.

5. Conclusion

In conclusion, the selected AG treatment generated rather convincing and yet preliminary long-term clinical efficacy when administered as an adjunct to conventional antihypertensive and antidiabetic therapy. The present study was the first to demonstrate that AG can generate favorable effects on pulse wave reflection in addition to systolic BP. This broadens our comprehension on the topic of ginseng and arterial stiffness, which commenced relatively recently and until now has not yielded direct evidence with regard to long-term effect of AG on arterial stiffness marker. Also, it draws our attention to the importance of raw material selection and compositional alteration of the ginseng root that can induce potentially significant differences in physiological response. Further long-term studies with different ginsenoside profiles, wide range of doses and larger sample size are needed before recommendations are formed for its use in management of hypertension in individuals with type 2 diabetes.

Disclosure

Vladimir Vuksan is a holder of an American (No. 7,326,404 B2) and Canadian (No. 2,410,556) patents for use of viscous fiber blend in diabetes, metabolic syndrome and cholesterol lowering; currently holds grant support for ginsneg research from the Canadian Diabetes Association, Canada and the National Institute of Horticultural & Herbal Science, RDA, Korea; receives remuneration as VP and part owner of Glycemic Index Laboratories, Inc. a contract research organization.

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