ORIGINAL CONTRIBUTION

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Efficacy and safety of American ginseng (*Panax quinquefolius* L.) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: a double-blind, randomized, cross-over clinical trial

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Abstract

Purpose Despite the lack of evidence, a growing number of people are using herbal medicine to attenuate the burden of diabetes. There is an urgent need to investigate the clinical potential of herbs. Preliminary observations suggest that American ginseng (*Panax quinquefolius* [AG]) may reduce postprandial glycemia. Thus, we aimed to evaluate the efficacy and safety of AG as an add-on therapy in individuals with type 2 diabetes (T2DM) controlled by conventional treatment.

Methods 24 individuals living with T2DM completed the study ($F{:}M = 11{:}13$; age $= 64 \pm 7$ year; BMI $= 27.8 \pm 4.6$ kg/m^2; HbA1c $= 7.1 \pm 1.2\%$). Utilizing a double-blind, cross-over design, the participants were randomized to receive either 1 g/meal (3 g/day) of AG extract or placebo for 8 weeks while maintaining their original treatment. Following a ≥ 4-week washout period, the participants were crossed over to the opposite 8-week treatment arm. The primary objective was HbA1c, and secondary endpoints included fasting blood glucose and insulin, blood pressure, plasma lipids, serum nitrates/nitrites (NOx), and plasominogen-activating factor-1 (PAI-1). Safety parameters included liver and kidney function.

Results Compared to placebo, AG significantly reduced HbA1c (-0.29%; $p = 0.041$) and fasting blood glucose (-0.71 mmol/L; $p = 0.008$). Furthermore, AG lowered systolic blood pressure (-5.6 ± 2.7 mmHg; $p < 0.001$), increased NOx ($+1.85 \pm 2.13$ µmol/L; $p < 0.03$), and produced a mean percent end-difference of $-12.3 \pm 3.9\%$ in LDL-C and $-13.9 \pm 5.8\%$ in LDL-C/HDL. The safety profiles were unaffected.

Conclusions AG extract added to conventional treatment provided an effective and safe adjunct in the management of T2DM. Larger studies using physiologically standardized ginseng preparations are warranted to substantiate the present findings and to demonstrate therapeutic effectiveness of AG.

ClinicalTrials.gov Identifier NCT02923453.

Keywords Ginseng · *Panax quinquefolius* · Diabetes mellitus · Blood pressure · Blood glucose · Cholesterol

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Uljana Beljan-Zdravkovic is sadly deceased. This article is in memory of Uljana whose expertise made a great contribution to the design of this study.

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Introduction

Diabetes has advanced as a global health epidemic. Despite a new emphasis on preemptive therapeutic approaches, management of type 2 diabetes (T2DM) remains challenging. The increased dependence on conventional treatments to cope with this burden has coincided with a dramatic rise in the use of herbs [1]. This has prompted calls for proof of their safety and efficacy, with rigorous clinical trials necessary to distinguish their potential. A systematic review of clinical trials of herbs and dietary supplements used for glycemic control in diabetes reported that, although shown to be safe, there is insufficient evidence to make conclusions about their efficacy [2]. Of the herbs studied, American ginseng (AG) appeared to have the strongest evidence from randomized controlled trials (RCTs) for anti-hyperglycemic activity [3–5].

Ginseng is an herb derived from several species of the plant family *Araliaceae* and genus *Panax* indigenous to Asia and North America, and has been valued for centuries by local cultures as a tonic and remedy for many ailments. 13 distinct species of ginseng have been identified; the most popular and most studied species being American and Asian ginsengs. Initially, in a series of acute, double-blind, placebo-controlled trials, we showed that a single batch of Ontario-grown American ginseng root consistently decreased postprandial glycemia by approximately 20%, both in people with T2DM [6, 7] and without [6, 8–11]. Although the mechanisms of action for the alleged effects of ginseng remain to be elucidated, there is growing evidence from experimental and clinical studies, indicating that AG may stimulate glucose-dependent insulin secretion [12, 13]. While preliminary, these findings advocate that AG's potential role in management of diabetes should be taken seriously and investigated further in longer term clinical settings [14].

To explore whether AG might have long-term therapeutic value, we studied the efficacy and safety of a systematically isolated AG extract in T2DM. The study was designed to test the effect of AG as an add-on therapy to conventional T2DM treatment, with a primary outcome of HbA1c and secondary outcomes including diabetes-related risk factors.

Materials and methods

Participants

The study was conducted on an outpatient basis in a single Canadian academic center (Risk Factor Modification Centre, St. Michael's Hospital, University of Toronto) with the participants recruited through local newspaper advertisements. Interested individuals meeting initial telephone screening criteria were invited for a clinic screening visit. Inclusion criteria were: age between 45 and 75 years, T2DM duration ≥ 1 year, BMI between 25 and 35 kg/m^2, and HbA$_{1c}$ between 6.5 and 8.5%. Excluded were patients on insulin therapy, those with self-reported impaired hepatic or renal function, medical history of clinically manifested diabetic complications, cigarette smokers, alcohol consumption (> 2 drinks per week), use of ginseng or other dietary supplement with possible hypoglycemic effects, and involvement in any other study. Patients who changed oral anti-hyperglycemic agents, blood pressure, or lipid lowering medication during the course of the study were excluded. The study was approved by the St. Michael's Hospital research ethics review board. This study was registered at ClinicalTrials.gov, identifier: NCT02923453.

Study design

The study represents an efficacy and safety trial that is conducted under optimal outpatient clinical and laboratory condition to allow tight control over participant's selection, treatment, data collection, and follow-up. The study utilized a randomized, double-blind, placebo-controlled, cross-over design and included two 8-week treatment arms, separated by a minimum 4-week washout period. Participants attended the clinic every 4 weeks (i.e., weeks 0, 4, and 8 of each treatment arm) for the duration of the study of 20 weeks. 3-day diet histories, anthropometric, laboratory, and clinical measurements, to assess efficacy and safety of study interventions, were collected at each study visit. At beginning, middle and end of the study, participants provided a symptoms diary to record adverse events. Left over supplements was collected to assess the adherence to the study interventions. Participants were encouraged to maintain their standard lifestyle, body weight, and a constant level of physical activity throughout the study. The randomization was performed using a computer-generated random number table, stratified according to sex and HbA$_{1C}$ created by a study statistician off-site. An individual otherwise not involved in the study performed blinding. The statistician remained blinded to the nature of study treatment until primary and secondary analyses were complete.

Intervention

Participants were asked to consume 1 g/meal, of cornstarch placebo (Canada Cornstarch™) or AG extract capsules, orally, 40 min preprandially, three times per day (3 g/day) for 8 weeks, while maintaining their original lifestyle and

pharmacotherapy. Both treatment and control were ground into dried powders and encapsulated in identical (500 mg) opaque capsules (Capsugel®): each treatment consisted of six capsules for a total of 3 g/day.

We selected an AG extract through a series of acute feasibility postprandial glycemic studies [5–11]. Generic AG with different ginsenoside compositions was administered in ranging doses (1–9 g) over a range of pre-prandial time-points (− 120 to 0 min) in healthy and T2DM individuals. We were able to identify a specific AG composition with reproducible and sustainable glycemic benefits confirmed in both healthy and individuals with T2DM. These findings resulted in the extract CNT 2000 (Chai-Na-Ta Corp., Langley, BC) containing 9.67% of total ginsenosides, with a ratio of Rb1–Rg1 of 23.44 and a protopanaxodial-to-protopanaxotrial ratio (PPD:PPT) of 3.03. Based on categorical analysis, ratio between PPD and PPT was indicated as the sole independent predictor of the effects on area under curve (AUC) for blood glucose and mean plasma glucose and 90 min and AUC plasma insulin found to be significant in categorical analyses [15].

American ginseng was derived from a representative sample of 3-year-old Ontario-grown ginseng (Ontario Ginseng Growers Association, Simcoe, ON, Canada). The extract was prepared by repeated extraction of dried whole AG root using approximately 70% ethanol to 30% water that derived a targeted ginsenoside composition. Liquid from the extraction was dried, milled into a fine powder, and encapsulated. Additional detail about the preparation of investigational product is considered proprietary by the manufacturer. The ginseng extract composition was analyzed for the four main PPD ginsenosides (Rb1, Rb2, Rc, and Rd) and two main PPT ginsenosides (Rg1 and Re) using the HPLC-UV techniques developed for the American Botanical Council Ginseng Evaluation Program [16]. The HPLC conditions included: chromatograph—Beckman HPLC system; column—a reverse-phase Beckman ultrasphere C-18, 5 μm octadecylsilane, 250 × 4.6 mm column; mobile phase—deionized water and acetonitrile; flow rate − 1.3 mL/min; and UV detection—a module 168 diode-array detector set at 203 nm. Final interventional extract contained the following concentrations of major ginsenosides (%): Rb1 (5.86), Rb2 (0.09), Rc (0.59), Rd (0.73), Re (2.15), and Rg1(0.25).

Study outcomes

The primary study objective was to determine whether an 8-week administration of AG extract as an add-on therapy would induce a significant change in HbA1c from baseline compared to the standard-of care. Secondary endpoints included change in fasting blood glucose and insulin, systolic and diastolic blood pressure, plasma lipids, markers of nitric oxide generation, and PAI-1 concentration.

Safety assessment

Safety parameters included markers of hepatic alanine amino-transferase (ALT) and renal (serum creatinine) function. Adverse events were documented and monitored throughout the trial.

Analytical assessment and assays

HbA1c was measured by TOSOH Hemoglobin Analyzer (TOSOH, Japan) using HPLC method (Core Lab, St. Michael's Hospital, Toronto). Fasting blood glucose was analyzed by a glucose oxidase method with Vitros 950 Analyzer (Johnson & Johnson, USA). Serum insulin concentration was determined by a double antibody radio-immunoassay method using commercial kits (Banting and Best Diabetes Centre Core Laboratory, the Toronto General Hospital, Toronto). Plasma plasminogen activator inhibitor-1 (PAI-1) was measured by the standard immunoassay kits. Serum NOx was measured by a chemiluminescence method using NO Analyzer (NOA, Sievers 270b, Boulder, CO, USA) at the Department of Medical Biophysics, the University of Western Ontario, London. Serum ALT and serum creatinine were determined by the standard methods by St. Michael's hospital core laboratory enzymatically. Measurements of blood pressure were recorded with the seated participant on the dominant arm using an automatic cuff oscillometric device (HEM-9000AI, Omron Healthcare, Japan). Serum creatinine and ALT were determined by the standard methods. 3-day diet histories were analyzed using the ESHA Nutrition and Fitness Software (Version 6.11, Salem OR, USA). Mean daily pill count was assessed as the total number of pills dispensed minus the number of capsules returned at each study visit.

Statistics

Repeated measures General Linear Model (GLM) ANCOVA was used to assess differences between and within intervention in the mean change from baseline in primary and secondary outcomes, in per-protocol analysis. When data did not meet normality and equal variance, Wilcoxon Signed-Rank Test approximated with continuity correction was used to test the difference. Correlations were determined using the Pearson correlation equation. The frequency of adverse events and symptomatic hypoglycemic episodes in the two treatment groups was composed using a proportional odds model. Changes in laboratory safety data were evaluated using Wilcoxon Signed-Rank Test. Participant characteristics were expressed as mean ± SD, while all other measurements were presented as mean ± SEM. $p < 0.05$ was

considered to be statistically significant. All analyses were performed on the SAS statistical package (SAS for Windows, version 6.0, SAS Institute, Cary, NC).

Based on our own and other groups observations from long-term ginseng studies in the primary efficacy endpoint, utilizing a cross-over design, to have 80% probability of detecting a 0.5% difference in HbA1c with 30% attrition rate, 38 participants needed to be enrolled, assuming an overall SD of 1.3%, with a two-tailed alpha of 5% [17, 18].

Results

The baseline characteristics of the participants are presented in Table 1.

A total of 459 interested individuals were screened by telephone. Those eligible were invited to visit the clinic for a screening visit and 38 individuals who met eligibility

Table 1 Baseline characteristics ($n = 24$)

Participant disposition (n)	
Screened	459
Randomized	38
Excluded (change in CVD risk factor medication)	10
Withdrawn	
Schedule conflict	2
Adverse events[a]	2
Completed	24
Baseline characteristics	
Age (years)	64 ± 7
Sex—M/F (n)	13/11
BMI (kg/m^2)	27.8 ± 4.6
Phase I randomization (placebo/AG)	11/13
Duration of diabetes	6.1 ± 5
HbA$_{1C}$ (%)	7.1 ± 1.2
Treatment of diabetes (n)	
Diet only	8
Metformin	1
Sulfonylurea	7
Sulfonylurea + metformin	8
Subjects with lipid lowering treatment (n)	9
Treatment of hypertension (n)	
Ca+ + channel blockers	5
ACE inhibitors	10
ARBs	2
β blockers	2
Diuretics	2
Combined treatment	5
Subjects with dietary supplements (no herbs) (n)	11

Data are means $\pm$ SD or n (%)

[a]The adverse events withdrawals are due to one case of headaches in test and one case of diarrhea in the control intervention

criteria were identified and enrolled. 24 completed the study. Reasons for attrition were: change in medication (10 total, 5 change in oral anti-hyperglycemic agents; 2 change in anti-hypertensive medication, 3 change in lipid lowering agents), 2 adverse events (1 experienced strong headaches during test arm and 1 experienced diarrhea during the placebo arm), and 2 had schedule conflicts. There were 13 males and 11 females with the mean age 64 ± 7 years, median duration of diabetes of 6.1 ± 5 years, and the mean BMI in the overweight range of 27.8 ± 4.6 kg/m^2. Eight participants were treated with diet only and 16 were receiving oral antihyperglycemic agents (8 on combined metformin and sulfonylurea, 1 on sulfonylurea, and 7 on metformin only).

Efficacy

At the end of the study, the primary endpoint HbA1c was lower on AG compared to placebo by $0.29 \pm 0.1\%$; $p = 0.041$ (Table 2). The fasting blood glucose was lowered on AG intervention relative to control, with a between-treatment difference of -0.71 ± 0.34 mmol/L, ($p = 0.008$). Serum insulin increased by approximately $33 \pm 21\%$ on AG compared to control; however, there was no significant between-treatment difference ($p = 0.127$). Systolic blood pressure was reduced on AG vs. placebo treatment at the end of study by 5.6 ± 2.7 mmHg ($p < 0.001$), while no difference in diastolic blood pressure was observed (-2.5 ± 1.4 mmHg, $p = 0.12$). Compared to control percentage, mean (SE) change at end of treatment on plasma lipids was as follows: LDL-C, -12.3% (3.9%) ($p < 0.003$); T-C, -9.0% (2.4%) ($p < 0.002$); TC/LDL-C, -11.8% (4.0%) ($p < 0.016$); and LDL-C/HDL-C -13.9% (5.8%) ($p < 0.009$). Likewise, serum NOx concentration was higher on AG vs. placebo, with a treatment difference of 1.85 ± 2.1 μmol/L ($p = 0.03$). American ginseng administration reduced fasting plasma PAI-1 from 47.8 ± 5.5 to 36.7 ± 4.7 ng/mL ($p = 0.007$), with no change on the placebo arm (35.6 ± 5.3 to 36.5 ± 4.1 ng/mL, $p = 0.836$), resulting in a non-significant between-treatment difference of 12.1 ± 6.0 ng/mL ($p = 0.057$). There was a significant inverse correlation in the percent end-value between NOx and HbA1c ($R = -0.42$, $p = 0.043$).

Other outcomes

Safety parameters

There was no difference in hepatic or renal function parameters found within and between treatments (Table 2).

Compliance

Participants maintained their body weight throughout the study and there were no significant differences between

Table 2 Mean (± SEM) changes in outcome measures after 8-week administration of American ginseng extract or control in 24 individuals with T2DM

Measurement	American ginseng extract			Control			p value between-treatment[‡]
	n	Baseline	8 weeks	n	Baseline	8 weeks	
Glycemic control (plasma)							
HbA$_{1c}$ (%)	24	7.13±0.21	7.01±0.25*'	24	7.26±0.22	7.28±0.21	0.041
Fasting glucose (mmol/L)	24	9.16±0.58	8.21±0.67*	24	8.38±0.48	8.74±0.51	0.008
Fasting insulin (pmol/L)	24	77.8±8.7	87.4±10.9	24	88.1±13.7	76.2±8.5	0.127
Mean blood pressure (mmHg)							
Systolic	24	137.1±3.6	126.1±3.8*	24	131.3±4.0	131.7±3.8	0.001
Diastolic	24	83.2±1.9	78.0±2.0*	24	80.8±2.1	80.4±2.1	0.123
Lipids (mmol/L)							
Total cholesterol	24	5.2±0.2	5.0±0.2	24	5.1±0.2	5.5±0.2	0.002
LDL cholesterol	24	3.3±0.2	3.1±0.2	24	3.2±0.2	3.6±0.2	0.003
HDL cholesterol	24	1.03±0.02	1.00±0.08	24	1.01±0.06	1.03±0.07	0.326
Total cholesterol/HDL cholesterol	24	5.4±0.2	5.2±0.3	24	5.3±0.3	6.1±0.3	0.016
LDL cholesterol/HDL cholesterol	24	3.4±0.2	3.2±0.3	24	3.4±0.2	3.9±0.3	0.009
Anthropometric measurements							
Body weight (kg)	24	79.7±3.3	79.1±3.1	24	79.7±3.4	79.5±3.2	0.454
Safety							
Urea (mmol/L)	24	6.0±0.4	5.7±0.2	24	5.2±0.4	5.7±0.2	0.953
Creatinine (μmol/L)	24	74.0±3.3	74.0±1.4	24	71.2±3.1	72.6±1.3	0.783
ALT (U/L)	24	25.6±2.8	25.6±1.6	24	32.5±2.6	26.5±1.5	0.167
Other end points							
Nitric oxide (μmol/L)	24	19.65±1.7	22.56±2.18	24	24.46±3.2	20.71±2.6	0.030
Plasminogen Activator Inhibitor (μg/mL)	24	47.8±5.5	36.7±4.7	24	35.6±5.3	36.5±4.1	0.057

Data are means ± standard error of the mean

SEM standard error of the mean, *ALT* alanine amino-transferase

*Significantly different from baseline within intervention as assessed with ANCOVA, $p < 0.05$

'Significantly different from placebo at week 8, $p < 0.05$

[‡]Between-treatment values were assessed with repeated measures ANCOVA with time as the repeated factor

the energy and macronutrient intake during the placebo (1769±102 kcal, 19.6±1.1 g protein, 28.8±2.3 g total fat, 51.3±3.3 g total carbohydrate, and 25.0±2.0 g fiber) and AG (1753±78 kcal, 19.6±1.1 g protein, 31.0±2.1 g total fat, 49.6±3.0 g total carbohydrate, and 22.8±1.9 g fiber) treatments. Returned capsule count was not different with 90 and 91% of prescribed capsules taken on test and control arms, respectively.

Discussion

The study demonstrated that oral co-administration of a particular AG preparation taken along with conventional therapy can enhance the management of T2DM. The glycemic benefits were accompanied with a reduction in systolic blood pressure, blood lipids, and increased nitric oxide generation possibly as a result of improved endothelial function, indicating that AG may contribute to better control of conventional and emerging cardiovascular disease risk factors.

While the level of reduction of HbA1c may represent a modest change, it approaches clinical relevance within the standards for anti-hyperglycemic agents which are required by the FDA to demonstrate an absolute change in HbA1c by ≥ 0.3% [19]. Furthermore, in a more recent study with empagliflozin, a drug shown to reduce composite CVD outcomes in type 2 diabetes, the reduction of HbA1C was 0.54% [20]. Support for clinical studies using ginseng of any type to improve glucose metabolism, including reduction of HbA1c and fasting blood glucose, is scarce and inconclusive. Some show a reduction of HbA1c in the range of 0.33–0.40% [18, 21], while others do not [17, 22]. In a recent systematic review and meta-analysis of 16 RCTs in the general population, ginseng showed modest lowering of fasting blood glucose and a tendency to reduce HbA1c in studies with a parallel design involving individuals with T2DM [23]. Similarly, the most recent systematic review and meta-analysis

evaluating the effect of ginseng on glycemic control in T2DM that includes 8 RCTs are in accordance with these results, showing glycemic, vascular, and lipidemic improvements [24]. Both groups concluded that there is a potential for ginseng in improving glucose metabolism with a level of uncertainty and a call for more clinical research on ginseng in diabetes. A reduction of 0.71 mmol/L in fasting blood glucose in the present study is in close agreement with 0.90 mmol/L cumulative reduction seen on nine studies conducted in T2DM population reported in a meta-analysis by Shishtar et al. [23].

Along with improved glycemic parameters, there was also an observable but insignificant increase in insulin secretion of approximately 33% ($p = 0.127$) suggesting a possible improvement in β-cell function. In a mechanistic acute study from our lab, we found an increase in glucose-stimulated insulin secretion after consuming the same batch of AG as used in this trial, where insulin secretion was raised by > 1.5-fold in the first 45 min following the 75 g oral glucose load in healthy individuals [13, 25]. This was interpreted as a possible increase in first release insulin secretion, a common abnormality in T2DM. Similarly, studies using various fractions of ginseng, reported an increase in insulin secretion and binding in diabetic mouse models at a level similar to that observed using sulfonylureas [12]. However, more mechanistic studies with insulin metabolism as primary objectives are needed.

The improvement in systolic blood pressure following the AG treatment ($- 5.6 \pm 2.7$ mmHg, $p < 0.001$ compared to control) represents a noteworthy therapeutic outcome, especially important in diabetes, since approximately 70% of these patients are living with hypertension. These findings are in agreement with a comparable study in T2DM utilizing a standardized American ginseng extract of similar composition that showed favorable reduction in systolic blood pressure and pulse wave reflection [26]. Contrary to that, our earlier long-term study in non-diabetic individuals with hypertension using American ginseng whole root exerted a neutral effect on mean 24 h ambulatory blood pressure following a 12-week intervention period [5]. Although reasons for the difference in results are not completely clear, differences in type of intervention (whole root vs. extract) and study population may have contributed. The blood pressure effect of varying ginsengs was assessed in a more recent systematic review and meta-analysis that pooled 17 RCT with 1381 participants. The analysis did not identify change in systolic or diastolic blood pressure following ginseng intervention, although subgroup analysis revealed a significant association between baseline systolic blood pressure values and treatment differences ($p < 0.04$) [27].

The present AG (CNT 2000 extract) treatment improved vascular function by reducing blood pressure, and possibly improved endothelial function as suggested by an increase in serum NOx ($1.85 \pm 2.13\%$, $p < 0.03$ compared to control) and, albeit insignificant, a reduction in plasminogen activator inhibitor-1. Nitric oxide is an important cellular-signaling molecule, where its reduced bioavailability is associated with endothelial dysfunction [28]. It has been suggested that in presence of ginseng metabolites, activity of endothelial NO synthase is increased [29]. A significant body of the literature supports that the NO-generating pathway is impaired in T2DM and is closely related to insulin resistance [30–32]. Possible link between improved NOx generation and improved glycemic control was also observed in this trial from a significant inverse correlation between percent end change in NOx generation and change in HbA1c ($R = -0.42$, $p < 0.05$).

It is interesting to observe a lipid lowering effect of AG extract that was at the level of reduction seen with some types of viscous dietary fiber [33]. The effect of ginseng on blood lipids has been reported in recent systematic review and meta-analysis, with significant reduction of total cholesterol, LDL-C and triglycerides, but no change in HDL-C [24]. On the contrary, a recent 12-week follow-up study administering 5 g/day of Korean red ginseng to newly diagnosed T2DM volunteers, observed no change in blood lipids, or in other metabolic parameters, except for a clinically irrelevant reduction in postprandial blood glucose at 30 min [34]. Reason for neutral results may not be completely surprising, because the study may have been underpowered and using a ginseng root with a ginsenoside composition of a PPD:PPT ratio of 1.65:1, which is below the suggested efficacy threshold applicable for different types of ginseng [13, 35]. Nonetheless, further research should explore this therapeutic aspect of ginseng in a clinical setting along with dose–response analysis and potential mechanistic explorations to better characterize the relationship. Currently, evidences of effects of ginseng and its components on cardiovascular risk factors are primarily based on traditional beliefs and preclinical research [36].

Neither the whole ginseng root preparations of different species nor their components have been linked to any serious adverse events in the literature [36], which has been reflected in our trial. The present investigation, although limited in safety assessment, is also in line with our previous observations, reporting on a more comprehensive safety profile of AG within an RCT setting [37].

Limitation

Some caution must be taken when drawing conclusions from the results of the present study and its implications for efficacy and safety. This includes possible methodological confounders related to the design and protocol. Study period of longer duration may provide a better estimate of changes in HbA1c levels. However, HbA1c is an exponentially

weighted average of the mean blood glucose, where the first 2 months already contribute to a major portion of the final HbA1c value [38]. This is reflected in the clinical practice guidelines, where 8–12 weeks are a recommended follow-up duration to monitor glycemic targets to anti-hyperglycemic agents [39].

A small sample size due to a high attrition rate may be a factor. More patients than expected were encouraged to change their treatment during the study intervention as the study coincided with findings from a large RCT advocating for more stringent diabetes control. Lower than anticipated sample size might have led to a type II error, especially where a trend towards ginseng-induced improvements such as fasting insulin ($p = 0.127$) and PAI-1 ($p = 0.057$) was observed. The present analysis highlights the need for an intent-to-treat analyses rather than per-protocol analyses in future investigations. Furthermore, the findings from this study may not be applicable to other types of ginseng or processing such as fermentation, because the composition of ginseng varies widely between available commercial products and extraction methodologies. Based on meta-analysis of ginsenoside composition across different preparations, variety and species, a coefficient of variation between-species and within-species of 26–112 and 22–133%, respectively, was found [40, 41]. The implication of this high variability in ginsenosides is that its efficacy of ginseng for glycemic control may be equally variable.

Strengths

The study has several important strengths. To our knowledge, this was the first study exploring efficacy and safety of an AG extract in T2DM management. In addition, this study provides promising information on multifaceted effects of AG with respect to glycemic, vascular, and lipid parameters. Another advantage is the application of a systematic method for selection of the study material, utilizing our herbal screening program with an aim to develop a standardized ginseng sample that is based on the physiological standardization of ginseng, to consider dose and time of administration, as well as testing the effect of different alcohol extraction preparations [15, 42].

Conclusion

These results suggest that the concurrent use of American ginseng as an adjunct to conventional T2DM treatment might be considered as a safe and valuable complimentary, add-on therapy for the management T2DM, and associated cardiovascular disease risk factors. Together with future effectiveness data, the results of the current study may provide important information to health agencies in formulating future guidelines on medicinal herbs for the management of T2DM and associated risk factors.

Compliance with ethical standards

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