Effect of coadministration of enriched Korean Red Ginseng (Panax ginseng) and American ginseng (Panax quinquefolius L) on cardiometabolic outcomes in type-2 diabetes: A randomized controlled trial

Jovanovski, Elena; Smirčić-Duvnjak, Lea; Komishon, Allison; Au-Yeung, Fei Rodney; Sievenpiper, John L.; Zurbau, Andreea; Jenkins, Alexandra L.; Sung, Mi-Kyung; Josse, Robert; Li, Dandan; ...

Source / Izvornik: **Journal of Ginseng Research, 2021, 45, 546 - 554**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1016/j.jgr.2019.11.005

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:788104

Journal of Ginseng Research 45 (2021) 546–554

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research/

Research Article

Effect of coadministration of enriched Korean Red Ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius* L) on cardiometabolic outcomes in type-2 diabetes: A randomized controlled trial

Elena Jovanovski [a,f], Lea Smircic-Duvnjak [b], Allison Komishon [a], Fei (Rodney) Au-Yeung [a,f], John L. Sievenpiper [a,c,d,e,f], Andreea Zurbau [a,f], Alexandra L. Jenkins [a], Mi-Kyung Sung [g], Robert Josse [d,f], Dandan Li [a,f], Vladimir Vuksan [a,c,d,f,*]

[a] Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada
[b] School of Medicine University of Zagreb, University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Zagreb, Croatia
[c] Li KaShing Knowledge Institute, St. Michael's Hospital, Toronto, Canada
[d] Division of Endocrinology & Metabolism, St. Michael's Hospital, Toronto, Canada
[e] Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, Toronto, Canada
[f] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada
[g] Department of Food and Nutrition, Sookmyung Women's University, Yongsan-gu, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 21 March 2019
Received in Revised form
25 September 2019
Accepted 4 November 2019
Available online 14 November 2019

Keywords:
Ginseng
Hypertension
Randomized controlled trial
Type-2 diabetes

ABSTRACT

Background: Diabetes mellitus and hypertension often occur together, amplifying cardiovascular disease (CVD) risk and emphasizing the need for a multitargeted treatment approach. American ginseng (AG) and Korean Red Ginseng (KRG) species could improve glycemic control via complementary mechanisms. Additionally, a KRG-inherent component, ginsenoside Rg3, may moderate blood pressure (BP). Our objective was to investigate the therapeutic potential of coadministration of Rg3-enriched Korean Red Ginseng (Rg3-KRG) and AG, added to standard of care therapy, in the management of hypertension and cardiometabolic risk factors in type-2 diabetes.

Methods: Within a randomized controlled, parallel design of 80 participants with type-2 diabetes (HbA1c: 6.5–8%) and hypertension (systolic BP: 140–160 mmHg or treated), supplementation with either 2.25 g/day of combined Rg3-KRG + AG or wheat-bran control was assessed over a 12-wk intervention period. The primary endpoint was ambulatory 24-h systolic BP. Additional endpoints included further hemodynamic assessment, glycemic control, plasma lipids and safety monitoring.

Results: Combined ginseng intervention generated a mean ± SE decrease in primary endpoint of 24-h systolic BP (−3.98 ± 2.0 mmHg, p = 0.04). Additionally, there was a greater reduction in HbA1c (−0.35 ± 0.1% [−3.8 ± 1.1 mmol/mol], p = 0.02), and change in blood lipids: total cholesterol (−0.50 ± 0.2 mmol/l, p = 0.01), non-HDL-C (−0.54 ± 0.2 mmol/l, p = 0.01), triglycerides (−0.40 ± 0.2 mmol/l, p = 0.02) and LDL-C (−0.35 ± 0.2 mmol/l, p = 0.06) at 12 wks, relative to control. No adverse safety outcomes were observed.

Conclusion: Coadministration of Rg3-KRG + AG is an effective addon for improving BP along with attaining favorable cardiometabolic outcomes in individuals with type 2 diabetes. Ginseng derivatives may offer clinical utility when included in the polypharmacy and lifestyle treatment of diabetes.

Clinical trial registration: Clinicaltrials.gov identifier, NCT01578837;

* Corresponding author. Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1M8, Canada.
E-mail address: v.vuksan@utoronto.ca (V. Vuksan).

https://doi.org/10.1016/j.jgr.2019.11.005
p1226-8453 e2093-4947/$ – see front matter

1. Introduction

Diabetes mellitus has emerged as a global health epidemic, often coexisting with hypertension which presents a multifold increased risk for cardiovascular disease (CVD) [1]. Within the context of comprehensive cardiovascular risk management, achieving blood pressure (BP) targets remains a clinical challenge, emphasized recently by stricter guidelines reaffirming the benefits of tight BP control [2]. Thus, novel combined treatment adjuncts, as part of a multifaceted approach, are required to attain adequate cardiometabolic control in this population.

With a diversified pursuit for effective management strategies, nonpharmacological approaches are receiving growing attention for meeting public health needs. Ginseng species have long been used for their therapeutic potential and consistent rank among the top five most commonly consumed herbs globally [3]. Two of the most common species, the American ginseng (*Panax quinquefolius* L.) and Korean Red Ginseng (*Panax ginseng* Meyer) are defined by a distinctive profile of dammarane-type glycosides called ginsenosides, purported to be the principal pharmacologically active constituents of ginseng. Although the phytochemical profile of ginseng has drawn significant research traction in the area of metabolic function, beneficial clinical correlation is limited.

Recent data suggests that AG and KRG may improve glycemic markers with two distinct but complementary mechanisms of action: AG appears to promote glucose-dependent insulin secretion, while KRG may increase insulin sensitivity [4,5]. Acutely, both AG and KRG were reported to flatten postprandial glucose concentrations without increased risk of hypoglycemia [6–8]. Furthermore, experimental evidence points to a vasodilatory effect of KRG-derived ginsenoside fractions [9–11]. The observed vascular relaxation stems from several proposed mechanisms largely mediated by nitric oxide stimulating pathways [10]. The most potent vasodilatory response in animal and *in vitro* models appears to be elicited by ginsenoside Rg3, present in KRG [11]. More recently, we have shown that oral administration of KRG enriched with ginsenoside Rg3 acutely improved BP and arterial stiffness in normotensive individuals [12].

Thus, we hypothesized that combining the glucose-lowering effects of both KRG and AG with the potential hemodynamic benefits of Rg3-enriched KRG (Rg3-KRG) may offer a multifaceted treatment advantage to diabetes patients with elevated BP. The objective of the present study, therefore, was to evaluate the efficacy and safety of a 12-wk coadministration of Rg3-KRG + AG extracts on systolic BP and in addition, explore associated cardiometabolic risk factors in individuals with type-2 diabetes managed by standard of care.

2. Research design and methods

2.1. Participants

Prospective participants were recruited using electronic and print advertisements, or through internal participant recruitment system of the patients within two participating university–affiliated hospital centers (St. Michael's Hospital Toronto, Canada, and KB Merkur Hospital, Zagreb, Croatia). Individuals were eligible to participate if they had a diagnosis of type-2 diabetes for ≥1 year, HbA1c values ≤ 8.5%, clinically diagnosed hypertension defined by the use of antihypertensive agents or seated systolic BP of ≥140 mmHg or diastolic BP ≥ 90 mmHg on two occasions and BMI<35 kg/m^2. Main exclusion criteria included: insulin therapy; systolic BP of ≥160 mmHg or diastolic BP ≥ 100 mmHg; heart failure; liver dysfunction; serum triglyceride >4.5 mmol/l; a history of coronary, arrhythmic or stroke events; inflammatory bowel disease; bleeding disorder; use of anticoagulants, antiplatelet, sympathomimetic or antidepressant drugs. All participants provided written informed consent. The study protocol met the regulatory framework of Health Canada and the institutional review boards of the participating sites. The trial was undertaken in compliance with Good Clinical Practice guidelines. The Clinicaltrials.gov identifier is NCT01578837.

2.2. Study design

We conducted a multicenter, randomized, placebo-controlled parallel design trial. Willing and eligible participants were randomized to either the treatment or placebo group with allocation created for each site. All participants and individuals involved in the analysis of the trial were blinded to treatment assignments for the duration of the study. Participants were scheduled to enter a placebo run-in phase for two wks to ensure that BP remained stable and allowed for protocol accustomization. Following the run-in phase, randomized participants entered either the test or control intervention for duration of 12 wks. Individuals were instructed to take study supplements orally in the morning, afternoon and evening each day prior to a meal, except on study visit mornings. Study visits occurred at baseline (week 0) and subsequently at four-wk intervals for the study duration. At each visit, participants attended the clinic after a 10–12 h fast and had anthropometrics taken, symptoms diaries and questionnaires completed, and outcome assessments performed. A >four-wk supply of study capsules was dispensed at every visit in two bottles (95 capsules each) to be started after completion of the baseline procedures. Changes to background antihypertensive and antihyperglycemic therapy and any adverse effects were recorded.

2.3. Interventions

Participants were randomized to either combined American ginseng (*P. quinquefolius*) and Rg3-enriched Korean Red Ginseng (*P. ginseng*) extract or Wheat-bran control. The combined ginseng supplement consisted of 1.5 g/day AG and 0.75 g/day Rg3-KRG standardized extracts (extracted to contain 75 mg of ginsenoside Rg3 and 375 mg total ginsenosides) or 2.25 g/day of control, contained in six gelatin capsules (3 × 500mg AG or control, 3 × 250 mg Rg3-KRG or control). There was no visual difference between the test and control capsules. The participants were instructed to take 2capsules t.i.d. Before each main meal. The AG was provided by the Ontario Ginseng Growers Association and extracted to 10% ginsenosides (Canadian Phytopharmaceuticals Corporation, BC, Canada). Dried AG roots were treated in 70% ethanol solution at 80°C for three h. The crude ginsenoside extract was filtered and combined filtrate is vacuum evaporated to appropriate volume. The final AG product had the following concentrations of major ginsenosides: Rb1 (36.76 mg/g), Rb2 (1.73 mg/g), Rb3 (4.44 mg/g), Rg1 (2.52 mg/g), Rc (10.87 mg/g), Rd (10.28 mg/g), Re (22.03 mg/g) and Rg3 (undetectable). The Rg3-KRG was prepared utilizing a proprietary technology by BTGin Corp. (Daejeon, Korea). Briefly, KRG rootlets underwent 50% and 85% ethanol extraction in consecutive steps. The extract was treated by enzyme and acid hydrolysis to amplify ginsenoside Rg3 content. Beta-glycosidase, produced from *Aspergillus niger*, which has cellulase, hemicellulase, glucosidase activity was used in acidic (pH 2.5~3.5) and thermophilic (65~80°C) conditions. To remove acid solution and concentrate Rg3, the reactant was passed through DIAION HP20 resin (Mitsubishi Chemical Industries, Tokyo, Japan) packed column. This was followed by evaporation to powder form under vacuum conditions. The final product containing 30% total ginsenosides had the following concentrations of major ginsenosides: Rb1 (3.77 mg/g), Rg1 (0.57 mg/

g), Re (1.86 mg/g), Rf (12.3 mg/g), Rb2 (1.24 mg/g), Rh1 (4.15 mg/g), Rc (0.99 mg/g) and Rg3 (100 mg/g). Individual ginsenosides were analyzed using high-performance liquid chromatography (HPLC). HPLC was carried out on a Liquid Chromatography (LC) system equipped with a quaternary gradient pump (Spectra 4000) and UV detector (Spectra 2000). A reversed-phase column (Hypersil gold C18, 100 mm 4.6 mm, internal 5 mm; Thermo Scientific) was used for quantitative determination of ginsenosides Rg3. The mobile phase consisted of acetonitrile and water with a flow rate at 1.6–2.5 mL/min and the detection wavelength was set at 203 nm. Control capsules contained standardized wheat bran provided by Rogers Foods Limited (Armstrong, BC, Canada). Quality control of all supplements was performed to comply with Health Canada regulations.

2.4. Outcome measurements

The prespecified primary endpoint was the 12-wk difference in 24-h systolic BP. Ambulatory BP monitoring was undertaken at baseline and study-end using a standardized cuff system (Spacelabs ABP Monitor 90207, Spacelabs Healthcare, WA, USA) placed on the nondominant arm. At baseline and week-12, automated readings were obtained at 20-min and 60-min intervals during daytime and night-time, respectively. Mean 24-h measurements were calculated by averaging BP readings collected within an hour and then averaging across the 24-h monitoring period for each patient. Ambulatory records were evaluated for quality according to prespecified criteria of >50% obtained recordings. Clinic BP was measured at each visit in the seated position by standard sphygmomanometry (Omron HEM-907XL, Omron Healthcare Inc., IL, USA). Three consecutive measurements were obtained one minute apart, and the values averaged for each visit. Exploratory hemodynamic endpoints included end differences in office BP, ambulatory diastolic, daytime and night-time BPs. Data on supplementary vascular measures were also obtained in this trial and will be reported separately.

Secondary glycemic endpoint was HbA1c at 12 wks, supported by exploratory fasting plasma glucose and insulin levels. Further exploratory endpoints included plasma lipid measures, in addition to safety outcomes. Laboratory measures were performed at baseline and at four-wk intervals thereafter. HbA1c analysis was performed using HPLC with the Tosh-HLC-723 analyzer (site 1) and Tina Quant turbidimetric inhibition immunoassay with the Cobas Integra 400 Plus analyzer (site 2), fasting glucose by a reaction rate method using the Beckman Synchron LX system (site 1) and Beckman Coulter AU680 (site 2), and insulin was analyzed using the Beckman Ultrasensitive Insulin Assay (Beckman Coulter, Brea, USA). Assays for safety measures [alanine aminotransferase (AST), creatinine, prothrombin time (PT), activated partial thromboplastin time (APTT) and International Normalized Ratio (INR)] and plasma lipid measurements [total cholesterol, HDL-C, non-HDL-C and triglycerides (TG)] were performed using standard methodology at the local hospital's clinic laboratory at each site. LDL-C was calculated using the Friedewald formula. Twelve-lead electrocardiograms, to assess the QT interval, were collected at weeks 4 and 12. Intervention compliance was assessed by using a returned pill count at each visit.

2.5. Statistical analysis

Statistical analyses were performed using the SAS statistical package version 9.2 (SAS institute Inc., Cary, NC, USA). Analyses were performed using the intent-to-treat (ITT) approach, which included all participants that were randomly assigned into the study who took at least one dose of the study intervention. PROC MIXED was used to determine between-treatment and within-treatment end-change in efficacy, safety and compliance endpoints at week-12 as the response variable, with baseline and center measures as covariates. Missing efficacy data were imputed using the PROC MIXED and MIANALYZE. Multiple imputation method assumes that the imputed values are randomly selected from the distribution of true missing values. Predictors of missingness at week-12 were used in the imputation. Chi^2 test was used to determine the differences in participants' categorical characteristics. We also conducted additional exploratory analyses for the effect of treatment by sex, antihypertensive medication type (NO stimulating vs. non-NO stimulating), antihyperglycemic medication type and baseline BP and HbA1c values. We tested for interaction of treatment BP effect with age (<60 vs. >60yrs), sex and BMI (<30 and >30 kg/m^2). Finally, in prespecified subgroup analysis, we evaluated the association of the 12-wk change in ambulatory BP values with corresponding baseline BP measures using linear regression analysis. Assuming a mean 24-h systolic BP difference from control of 4.7 mmHg [13] and a standard deviation of 6.8 mmHg, at a significance level of $\alpha = 0.05$ and $1\text{-}\beta = 0.8$, a total of 68 participants were required. With an estimated 20% attrition rate, a sample size of 82 participants or 41 per treatment group were to be recruited as per entry criteria.

3. Results

3.1. Participants

A total of 1,360 individuals were prescreened by phone out of which 361 individuals were assessed for eligibility (Fig. 1). Of these, 85 participants were randomly assigned to receive combined AG&Rg3-KRG intervention or control. Five participants discontinued the study in the run-in phase before receiving the study intervention (4 participants failed to attend the baseline measurement; 1 participant discontinued for medical reasons), resulting in 80 participants for which data was available at baseline to undertake analysis (modified ITT). Seventy-eight completed the entire study protocol following run-in, with the attrition rate of 3%. Baseline demographic characteristics are summarized in Table 1 and were similar across the treatment groups. There were no significant differences in baseline covariates between the two centers (data not shown). Most of the participants were receiving an oral antihyperglycemic agent (98%) and antihypertensive agent (96%) at baseline (http://hyper.ahajournals.org.myaccess.library.utoronto.ca/content/56/5/824.long, Table 1). Metformin was taken by 96% of participants where 62% were also on a DPP-4 inhibitor. In addition, 32 participants (39%) were receiving ≥2 antihypertensive drugs. Sixty-six percent of patients were on lipid lowering medication. Linear regression analysis revealed a significant negative association between intervention differences with ginseng and baseline systolic BP ($R^2 = 0.24$, $p < 0.001$). However, there were no significant interactions between treatment groups and sex, age, BMI, baseline BP or HbA1c or antihypertensive medication with respect to BP.

3.2. Office and 24-h ambulatory BP

Administration of AG&Rg3-KRG for 12 wks achieved a mean reduction in 24-h systolic BP of −3.98 ± 2.0 mmHg ($p = 0.03$) relative to control (Fig. 2). No within-treatment change from baseline to the end of 12 weeks in mean 24-h systolic BP was observed for either the control group (1.08 ± 2.4 mmHg, $p = 0.65$) or combined ginseng group (−1.70 ± 2.2 mmHg, $p = 0.44$). Participants receiving AG&Rg3-KRG also had greater reduction in daytime systolic BP (−4.47 ± 2.1 mmHg, p = 0.03), but not in night-

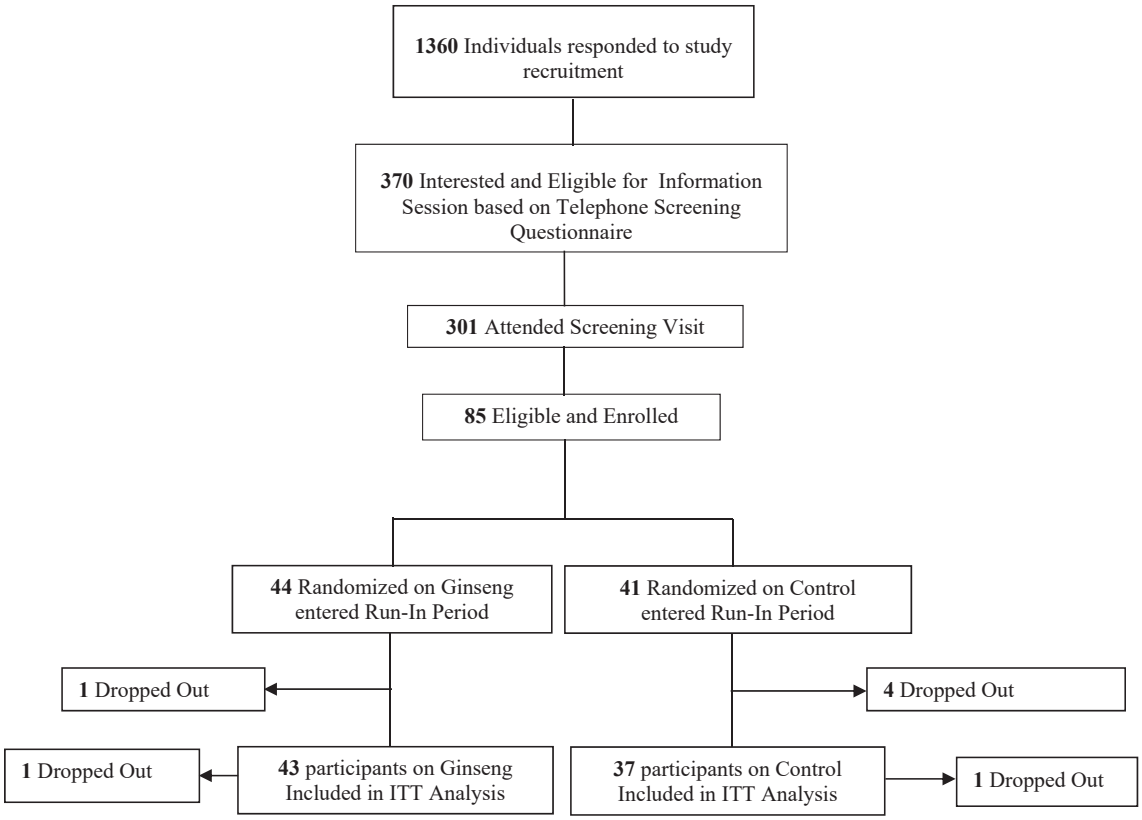

Fig. 1. Study flowchart.

Table 1
Baseline characteristics of study participants included in the ITT analysis.

Participant characteristics	Control	AG + Rg3-KRG	*p*
Sample size (*n*)	37	43	
Male: Female (*n*)	22:15	27:16	
Age (years)	60.58 ± 6.9	59.44 ± 7.4	0.88
BMI (kg/m^2)	29.66 ± 4.3	28.62 ± 3.4	0.17
Duration of diabetes (years)	8.75 ± 6.2	9.05 ± 6.6	0.66
Systolic BP (office) (mmHg)	131.72 ± 14.4	130.60 ± 13.3	0.51
Diastolic BP (office (mmHg)	74.60 ± 12.1	76.59 ± 9.7	0.36
24-h Systolic BP (mmHg)	126.75 ± 9.8	124.12 ± 12.2	0.31
24-h Diastolic BP (mmHg)	73.22 ± 7.7	74.86 ± 7.0	0.64
Heart rate (bpm)	70.37 ± 11.6	68.63 ± 11.1	0.60
HbA1c (%)	7.07 ± 0.7	6.87 ± 0.7	0.36
Fasting blood glucose (mmol/L)	7.61 ± 1.7	7.77 ± 1.4	0.44
Total cholesterol (mmol/L)	5.12 ± 0.8	5.09 ± 1.2	0.68
LDL-cholesterol (mmol/L)	2.90 ± 0.7	2.88 ± 1.0	0.78
HDL-cholesterol (mmol/L)	1.28 ± 0.2	1.28 ± 0.3	0.88
Triglycerides (mmol/L)	2.16 ± 1.1	2.27 ± 1.3	0.74
Medication use			
Antihypertensive No. of medications	97%1.6	94%1.6	
ACE inhibitor *n* (%)	24(64.8)	20(46.5)	0.25
ATII receptor blocker *n* (%)	9(25.0)	11(26.5)	0.89
Diuretic *n* (%)	13(35.1)	10(23.2)	0.33
Beta-blocker *n* (%)	8(21.6)	10(23.2)	0.64
Ca^{2+} channel blocker *n* (%)	15(40.5)	13(30.2)	0.28
Other *n* (%)	3(8.1)	3(6.9)	0.45
Antihyperglycemic No. of medications	100%1.9	99%1.7	
Metformin *n* (%)	36(97.4)	42(96.9)	0.48
DPP-4 inhibitor *n* (%)	27(72.9)	22(51.2)	0.11
GLP-1 agonist *n* (%)	2(5.4)	2(4.2)	0.88
Sulphonylurea *n* (%)	13(35.1)	10(23.2)	0.19
Other *n* (%)	2(4.34)	0(0.0)	

Data are presented as mean + SD. Significance shown in the last column for control vs. Rg3- KRG + AG. Abbreviations: BMI-Body mass index; BP-Blood pressure; LDL-Low density lipoprotein; ACE-Angiotensin converting enzyme; Ca^{2+}-Calcium; ATII-Angiotensin II; DPP-4-Dipeptidyl peptidase-4; GLP-1-Glucagon like peptide-1;No. – num.

time systolic BP (−2.52 ± 2.8 mmHg, $p = 0.37$). Meanwhile, no differences were observed in mean 24-h-, daytime- or night-time-diastolic BP (−0.96 ± 1.6 mmHg, $p = 0.54$; −1.54 ± 1.7 mmHg, $p = 0.34$; −0.23 ± 2.1 mmHg, $p = 0.91$, respectively) when compared with control. Changes in 24-h ambulatory BP parameters for the two groups are displayed in Table 2.

Based on mean sitting office BPs recorded at week-12, systolic BP decreased in the ginseng group by −5.22 ± 2.6 mmHg ($p = 0.02$) compared with the baseline values; no change was evident in the control group (−0.91 ± 2.9 mmHg, $p = 0.76$), with a between treatment effect of −4.46 ± 2.5 mmHg ($p = 0.07$). A similar pattern was observed with office diastolic BP, with a reduction from baseline to the end of 12 weeks in the ginseng treatment arm (−6.32 ± 2.2 mmHg, $p = 0.001$) and not in the control arm (−2.22 ± 2.4 mmHg, $p = 0.36$). No difference between interventions was observed in the office diastolic BP (−2.41 ± 2.2 mmHg, $p = 0.26$).

Ginseng supplementation was associated with greater reductions in mean 24-h BP and office BP in individuals with higher baseline BP ($R^2 = 0.24$, $p < 0.01$). However, the changes in the 24-h systolic BP were similar in subgroup analysis by gender (male vs. female), age (≤60 vs. > 60 years), BMI (≤25 kg/m^2 vs. >25 kg/m^2), baseline BP and HbA1c values, and antihypertensive or anti-hyperglycemic medication type.

3.3. Glycemic control

A 12-wk administration of Rg3-KRG + AG led to a significant treatment difference in HbA1c levels of −0.35 ± 0.2% ($p = 0.02$), where change from baseline of −0.25 ± 0.2% ($p = 0.02$) was observed in the combined ginseng group and no change in the control group (0.09 ± 0.2%, $p = 0.61$) (Table 2). Fasting plasma

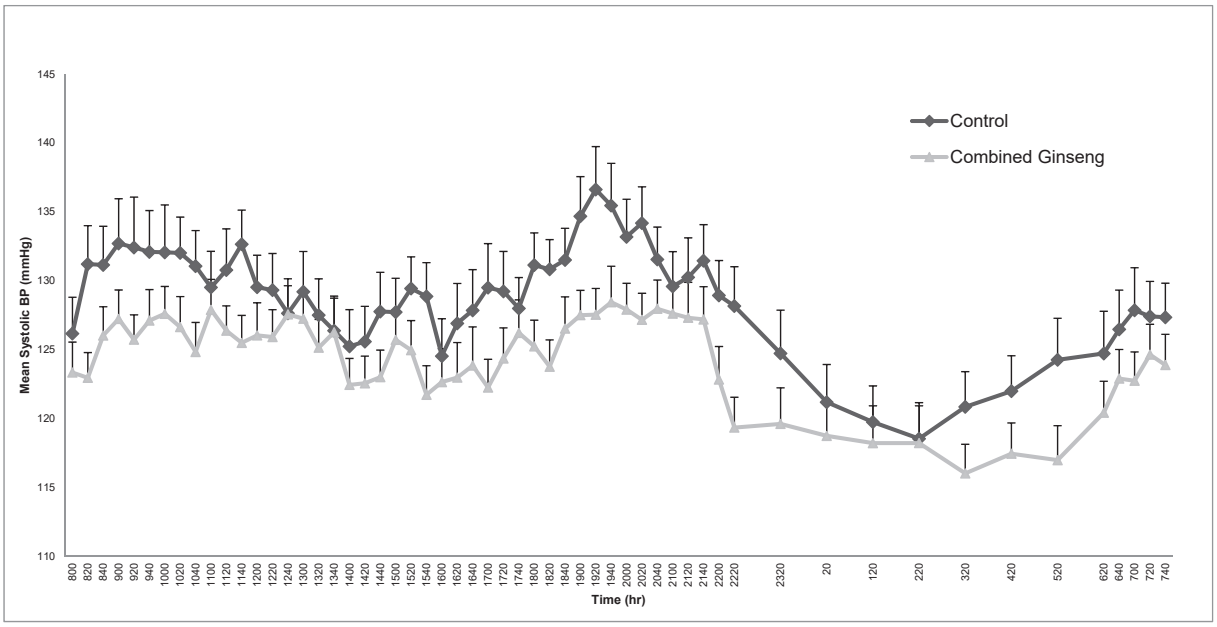

Fig. 2. Mean absolute 24-h systolic blood pressure profile at week-12 in participants with type-2 diabetes following either a control or combined ginseng (Rg3-KRG + AG) intervention. Abbreviations: BP-Blood Pressure; Error bars indicate SE; Grey diamond – Control; Black triangle– Combined ginseng.

glucose was not affected by the ginseng intervention relative to control (treatment difference: −0.02 ± 0.3 mmol/l, $p = 0.95$). Similarly, no difference in fasting insulin at 12 weeks was observed between treatment groups (2.72 ± 18.7 pmol/l, p = 0.88).

3.4. Lipids

At study end, the reduction of the combined ginseng versus control treatment was significantly greater for total cholesterol (treatment difference −0.50 ± 0.2 mmol/l ($p = 0.01$) and for non-HDL (−0.54 ± 0.2 mmol/l, $p = 0.01$), but approaching significance for LDL-C (−0.35 ± 0.2 mmol/l, $p = 0.06$). Similarly, mean TG levels were significantly reduced in the ginseng group by −0.43 ± 0.2 mmol/l ($p = 0.02$), relative to control. No difference was observed in HDL-C (0.06 ± 0.04 mmol/l, $p = 0.19$).

3.5. Safety variables

Oral intervention was well tolerated. There were no serious adverse events and no differences in adverse events

Table 2
Mean outcomes at wweek-0 and wweek-12 and changes in efficacy outcomes for all participants ($n = 80$) in ITT approach, by treatment group

	Control				Ginseng				Ginseng vs. control	p
	Week 0	Week 12	Change from baseline	p	Week 0	Week 12	Change from baseline	p		
Primary:										
24-h Systolic BP	127.14 ± 1.7	128.22 ± 1.7	1.08 ± 2.4	0.65	123.46 ± 1.6	121.76 ± 1.6	- 1.70 ± 2.2	0.44	- 3.98 ± 2.0	0.044
Secondary:										
HbA1c (%)	7.07 ± 0.1	7.15 ± 0.1	0.09 ± 0.2	0.61	6.86 ± 0.1	6.61 ± 0.13	- 0.25 ± 0.2	0.15	- 0.35 ± 0.2	0.019
Exploratory:										
Ambulatory Blood Pressure (mmHg)										
24-h Diastolic BP	73.69 ± 1.3	74.66 ± 1.3	0.96 ± 1.8	0.59	73.97 ± 1.1	73.33 ± 1.1	- 0.65 ± 1.5	0.67	- 0.96 ± 1.6	0.541
Daytime Systolic BP	29.50 ± 1.8	129.95 ± 1.8	0.45 ± 2.5	0.86	125.51 ± 1.5	123.12 ± 1.6	- 2.39 ± 2.2	0.28	- 4.47 ± 2.1	0.033
Daytime Diastolic BP	76.08 ± 1.3	76.41 ± 1.3	0.32 ± 1.9	0.86	75.58 ± 1.1	74.41 ± 1.1	−1.18 ± 1.6	0.46	−1.54 ± 1.7	0.364
Night-time Systolic BP	117.36 ± 1.7	121.32 ± 1.7	3.95 ± 2.4	0.10	114.29 ± 2.1	117.59 ± 2.2	3.30 ± 3.1	0.29	−2.52 ± 2.8	0.369
Night-time Diastolic BP	64.83 ± 1.4	68.05 ± 1.5	3.22 ± 2.1	0.12	65.91 ± 1.3	68.37 ± 1.3	2.46 ± 1.89	0.19	−0.23 ± 2.1	0.914
Office Blood Pressure										
Office Systolic BP (mmHg)	131.72 ± 2.1	132.63 ± 2.1	0.91 ± 2.9	0.76	134.68 ± 1.8	129.46 ± 1.8	−5.22 ± 2.6	0.02	−4.46 ± 2.5	0.071
Office Diastolic BP (mmHg)	78.33 ± 1.7	76.11 ± 1.7	- 2.22 ± 2.4	0.36	81.58 ± 1.5	75.27 ± 1.5	−6.32 ± 2.2	0.001	−2.41 ± 2.2	0.265
Heart Rate (bpm)	69.1 ± 2.7	69.3 ± 2.3	0.34 ± 4.1	0.93	69.7 ± 2.6	72.3 ± 2.1	2.98 ± 4.0	0.45	3.99 ± 2.1	0.060
Glycemic Measure										
Fasting Glucose (mmol/L)	7.61 ± 0.2	8.03 ± 0.2	0.42 ± 0.3	0.22	7.76 ± 0.2	7.99 ± 0.2	0.22 ± 0.3	0.26	−0.02 ± 0.3	0.946
Fasting Insulin (pmol/L)	80.92 ± 13.7	97.64 ± 14.2	16.72 ± 19.8	0.40	69.75 ± 10.2	93.78 ± 10.9	24.03 ± 14.8	0.10	2.72 ± 18.7	0.884
Lipids										
Total C (mmol/L)	5.12 ± 0.2	4.94 ± 0.2	−0.18 ± 0.2	0.45	5.09 ± 0.2	4.47 ± 0.2	−0.62 ± 0.2	0.01	−0.5 ± 0.2	0.007
LDL-C (mmol/L)	2.90 ± 0.1	2.74 ± 0.1	−0.17 ± 0.2	0.43	2.88 ± 0.1	2.40 ± 0.1	−0.48 ± 0.2	0.03	−0.35 ± 0.2	0.062
HDL-C (mmol/L)	1.28 ± 0.04	1.25 ± 0.04	−0.03 ± 0.1	0.54	1.29 ± 0.04	1.31 ± 0.04	0.02 ± 0.1	0.70	0.06 ± 0.04	0.187
Non-HDL-C (mmol/L)	3.84 ± 0.2	3.69 ± 0.2	−0.15 ± 0.2	0.50	3.80 ± 0.2	3.16 ± 0.2	−0.64 ± 0.2	0.01	−0.54 ± 0.2	0.009
Triglycerides (mmol/L)	2.16 ± 0.2	2.14 ± 0.2	−0.02 ± 0.3	0.93	2.26 ± 0.2	1.78 ± 0.2	−0.49 ± 0.2	0.06	−0.43 ± 0.2	0.017

All values are mean ± SE. Abbreviations: HbA1c-glycated hemoglobin A1c; BP-blood pressure; C-cholesterol; LDL-low density lipoprotein; HDL-high density lipoprotein; Missing data were obtained by five-fold averaged Multiple Imputations. The *p*-values for change from baseline determined using Least Squares Means in PROC MIXED. The *p*-values in the last column indicate the comparison between control and ginseng at 12 weeks corrected for center and baseline by ITT analysis using PROC MIXED.

between the two groups. Commonly reported adverse events included headache (three participants on ginseng and four control), nausea (two in ginseng and three in the control) and abdominal discomfort (six in ginseng and four in control) of transient nature, with no differences in number of events between treatment arms ($p = 0.62$).

Table 3 displays measured safety variables. There was no significant difference between the ginseng treatment and control with respect to changes in creatinine (-1.17 ± 1.6 mmol/l, $p = 0.47$), ALT (0.46 ± 2.2 U/l, $p = 0.92$) and the QT interval (0.62 ± 5.5 seconds, $p = 0.89$). Furthermore, hematological measures of PT (-0.06 ± 0.05 seconds, $p = 0.22$), APTT (0.05 ± 0.5 seconds, $p = 0.91$) and INR (0.002 ± 0.02, $p = 0.94$) did not differ between the combined ginseng and control. Overall compliance, as assessed by manual pill count, was $94.3 \pm 9.2\%$ in the treatment arm and $96.3 \pm 9.3\%$ in the control arm.

4. Discussion

Combination therapy has been advocated as a more effective means to meet clinical targets in the contemporary management of type-2 diabetes. The present study supports our hypothesis that coadministration of Rg3-KRG + AG for 12 weeks can result in improvement in BP in already treated type-2 diabetes patients with hypertension. Additional benefits included tighter glycemic control and reduction in plasma lipids with no adverse safety concerns.

The mean reduction in 24-h systolic BP of −4.0 mmHg over 12 weeks is clinically meaningful, particularly against the backdrop of antihypertensive therapy in this subject group. Systolic BP offers consistent and proportional CVD risk decrease in type-2 diabetes, where a 5 mmHg change results in a pooled estimate of 13% stroke reduction in BP lowering trials [14,15]. Improvement of BP is proposed to have a greater potential to reduce CVD than lowering plasma glucose concentrations in this population, thus representing a relevant primary therapeutic target [16]. Importantly, the 24-h BP reduction was not accompanied by an increase in heart rate and appears to be attributed to change in daytime rather than night-time BP, possibly an effect of 3x/day administration of Rg3-ginsensoide component and a reported, short half-life of its metabolites (0.46 ± 0.1 hours) [17]. The achieved ambulatory BP reduction is similar to that of office BP (i.e., −4.0 mmHg vs. −4.4 mmHg); nevertheless, the difference in office BP only approached statistical significance ($p < 0.07$) on account of large variability in the measure. The use of ambulatory BP monitoring in this trial, as an established better predictor of clinical outcomes than conventional office BP, offers an advantage of providing a more accurate estimate of true vascular benefits, underscoring the importance of ambulatory BP monitoring for defining BP control [18].

Selection of Rg3-enriched KRG as a complementary agent stems from a line of investigations into the vascular effects of this ginseng species. We have previously shown that the effect of KRG supplementation on flow-mediated vasodilation and pulse wave reflection was attributable to the ginsenoside fraction of the root [12]. In particular, ginsenoside 20(S) Rg3 appears most potent to induce nitric oxide–driven vasodilatation *in vivo* [19] and may attenuate the rise in intracellular calcium levels [20], while a preliminary evaluation of Rg3-KRG in hypertensive rats demonstrated significant improvement in BP [21]. A pilot study of single oral bolus dose administration of 400 mg Rg3-KRG in humans corroborated preclinical evidence with attained reductions in hemodynamic indices [12,21]. Furthermore, the same formulation of Rg3-KRG, assessed over eight weeks, may effectively improve erectile dysfunction offering additional support for the underlying vasodilating activity of Rg3-KRG [22]. The antihypertensive effect of Rg3 might be also exerted through the inhibition of angiotensin-converting-enzyme thereby modulating the activity of the renin-angiontensin system. Concurrent to the observed BP benefit, the combined ginseng supplementation resulted in a reduction of HbA1c level, where baseline concentration was proportional to HbA1c decline. The observed mean difference of 0.35% is within the range of >0.3%, proposed by the FDA guidelines as clinically meaningful lowering of HbA1c [23]. The modest decrease, which was adjunctive to oral antihyperglycemic agents, may be particularly relevant in patients who are near to achieving their treatment goal.

The choice of coadministration of two ginseng species rests with the understanding that they differentially affect glycemic control. Our group has previously shown that 3 g KRG administration resulted in 33% increase in both, HOMA-IS and oral glucose challenge–derived insulin sensitivity indices, over 12 weeks [4]. Several pathways are implicated, including modulation of glucose transport via glucose transporter protein and regulation of glucose disposal via glycolytic enzymes, further supported by the primary effect of KRG in intracellular signaling pathways [24,25]. Conversely, 6 g AG supplementation, improved HbA1c by $0.29 \pm 0.04\%$ (3.2 ± 0.4 mmol/mol), which was concomitant with a 30% rise in fasting insulin without associated weight gain or hypoglycemia [26], a finding reproduced in this study. The postprandial effect of AG on glucose-stimulated insulin secretion was observed previously [27]. Preclinical evidence also suggests enhanced insulin release in diabetic mice fed with AG, underwritten by morphological evidence of islet area increase [28,29]. The reduction in HbA1c using combined ginseng appears stronger than those noted previously using single ginseng supplementation. However, lack of direct comparison and factors such as concomitant therapy preclude an interpretation beyond a speculative one.

The observed decrease in HbA1c was not reflected in changes in fasting glucose, despite a noted reduction in our previous trial using

Table 3
Mean outcomes at week 0 and week 12 and changes in safety outcomes for all participants in ITT approach (n = 80), by treatment group

	Control				Ginseng				Ginseng vs. control	
Safety measures	Week 0	Week 12	Change from baseline	*p*	Week 0	Week 12	Change from baseline	*p*		
Creatinine (mmol/L)	74.08 ± 2.3	71.46 ± 2.3	−2.62 ± 3.2	0.41	74.63 ± 2.4	72.63 ± 2.5	−2.00 ± 3.5	0.56	−1.17 ± 1.6	0.47
Alanine aminotransferase (U/L)	28.61 ± 2.2	26.54 ± 2.3	−2.07 ± 3.2	0.51	31.24 ± 2.7	27.64 ± 2.7	−3.60 ± 3.9	0.35	0.46 ± 2.2	0.92
QT Interval (s)	400.47 ± 4.2	406.66 ± 4.3	6.19 ± 6.0	0.31	387.24 ± 4.2	398.31 ± 4.2	11.07 ± 5.9	0.06	0.62 ± 5.5	0.89
International normalized ratio	1.04 ± 0.01	1.04 ± 0.01	-−0.00 ± 0.01	0.84	1.04 ± 0.01	1.04 ± 0.01	0.00 ± 0.01	1.00	0.00 ± 0.02	0.94
Prothrombin time (s)	2.81 ± 0.05	2.82 ± 0.05	0.01 ± 0.1	0.84	1.82 ± 0.03	1.79 ± 0.03	−0.02 ± 0.04	0.61	0.05 ± 0.5	0.91

All values are mean ± SE. Abbreviations: QT interval-start of Q wave to end of T wave on the 12-lead electrocardiogram; Missing data were obtained by five-fold averaged Multiple Imputations. The *p*-values for change from baseline determined using Least Squares Means in PROC MIXED. The *p*-values in the last column indicate the comparison between control and ginseng at 12 weeks corrected for center and baseline by ITT analysis using PROC MIXED.

the AG root [5] and observations from a metaanalysis reporting a pooled fasting glucose lowering effect across ginseng sources [30]. However, resultant HbA1c values, although partially determined by fasting glucose, are thought to more strongly reflect postprandial glycemia [31]. Both AG and KRG have repeatedly been demonstrated to lower plasma glucose area under the curve ranging from 26% to 38% that were consistent across different doses (3–12 g) and times of administration (i.e., immediately or 40 min preprandially) [6], and may therefore have been the main mechanism of the HbA1c reduction seen in this study.

We observed a reduction in plasma lipid concentrations, including total cholesterol, non-HDL-cholesterol and triglycerides and a tendency toward lower LDL-C. Non-HDL-C is a particularly desirable target in individuals with diabetes characterized with elevated triglycerides [32]. A recent systematic review and meta-analysis pooling RCT data on lipid outcomes illustrated reductions in total, LDL-C and triglycerides in favor of ginseng, but no change in HDL-C [33]. Plausibly, the steroidal structure of triterpene saponins may act to modify gene transcription, protein synthesis and hepatic cholesterol production via inhibition of HMG-CoA reductase [34,35]. It appears that the effect on lipids is not specific to our selected intervention types as the signal emerges across different species and preparations [26]. While intriguing, these findings remain exploratory and necessitate more direct investigation.

The adverse events and selected biochemical safety markers in the ginseng group were similar to those noted with the control. These data are relevant given that the quantity of total ginsenosides present in the intervention, 375 mg/day, is in the uppermost range of those administered to humans in RCT settings. Mucalo et al (2014) provided comprehensive evidence in type-2 diabetes on the safety profile of three-month supplementation with AG extract standardized to 10% of ginsenosides, as used in our trial [36]; conversely, no clinical data on ginsenoside Rg3-enriched KRG was available. Accordingly, our results contribute to the current understanding of the clinical toxicology related to ginseng use and remain in concordance with the previous reports on generic *P. ginseng* monopreparations [37].

While preliminary, our study provides support for the potential clinical utility of promising herbal supplements as adjuncts to standard care. Use of botanical agents offers a distinct advantage because of its biochemical complexity and the possibility to act on multiple metabolic targets [38]. Conversely, lack of standardization and high compositional variability, as we demonstrated both between and within ginseng species and quantification assays, may prove to be prohibitive in their use as an alternative treatment option [39]. Hence, rigorous efficacy-founded component standardization of herbal supplements is a top priority to facilitate a reliable physiological response.

Our study has strength in its rigorous application of a controlled, adequately powered double-blind protocol and use of a well-characterized, reproducible intervention, derived from systematic preliminary screening studies. A high retention rate increases generalizability of our findings from ITT analysis. We opted to use a pragmatic, translational study design by selecting a population of participants with type-2 diabetes, who are already on medication and in whom assessed risk factors were clinically optimized. We further opted to use 24-h ambulatory BP recordings as the primary outcome, minimizing confounders of office BP measures to allow for more coherent characterization of BP.

There are several limitations of the current study. First, use of the intervention capsules (i.e., six/day) may add to the polypharmacy burden, despite the reassuring compliance (95%) in the outpatient study setting. Second, the bioactivity of ginseng varies across different preparations and modes of intake and extrapolating the efficacy and safety endpoints to other ginseng preparations, therefore, poses a challenge. Similarly, the choice of ginseng dose was limited by the availability of previous data and regulatory controls; we are thus unable at this time to define a dose-response relationship. Third, lack of direct comparison of individual ginseng species in the trial precludes comprehensive assessment of respective additive contributions. Fourth, using a time point–specific end point at week-12 for office BP instead of the change of BP over the entire duration of the trial did not use all of the data collected. Finally, the glycemic endpoints were analyzed within respective centers, introducing a source of measurement variability. Future research must further consider these points moving forward.

5. Conclusion

The present study provides quality evidence that combining botanicals, Rg3-KRG + AG, with purported complementary activity, can promote clinically meaningful changes in BP when added to standard therapy in type-2 diabetes. Further changes in exploratory glycemic and lipid endpoints provide additional support for the overall cardiometabolic benefits. Subsequent efforts should focus on further optimization of ginseng components and its reproducibility for development of viable therapeutic entities. Given the staggering diabetes prevalence frequently clustered with hypertension and dyslipidemia, such promising multitargeted risk reduction aids should be increasingly sought to assist in alleviating CVD risk.

Funding

The trial was funded by the Canadian Diabetes Association Grant-in–Aid funding, a contribution from BTGin Corp., Korea, and a donation from the Diabetes Alternative Research and Healthcare Foundation. Ontario Ginseng Growers provided an in-kind donation of the raw, Ontario-grown *P.quinquefolius* root. JL Sievenpiper was funded by a PSI Graham Farquharson Knowledge Translation Fellowship, Canadian Diabetes Association (CDA) Clinician Scientist award, CIHR INMD/CNS New Investigator Partnership Prize, and Banting & Best Diabetes Centre Sun Life Financial New Investigator Award. None of the sponsors had a role in any aspect of the present study, including design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, approval of the manuscript or decision to publish.

Authors' contributions

All authors participated in the trial design. AK, LDS and EJ took part in carrying out the trial and the data collection. FAY, EJ and AK took part in the data analysis. EJ, AK, VV and LZ prepared the manuscript draft. All authors interpreted the data. All authors read the manuscript critically and approved the submitted version.

Declaration of competing interest

V Vuksan holds an American (No. 7,326,404 B2) and Canadian (No. 2,410,556) patent for use of viscous fiber blend in diabetes, metabolic syndrome and cholesterol lowering. VV was partial owner of Glycemic Index Laboratories, Inc. (Toronto, ON, Canada) during 2004–2015**.**

JL Sievenpiper has received research support from the Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle

Nutritional Research Fund at the University of Toronto, and The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers). He has received speaker fees and/or honoraria from Diabetes Canada, Canadian Nutrition Society (CNS), Dr. Pepper Snapple Group, Dairy Farmers of Canada, Nutrition Foundation of Italy (NFI), C3 Collaborating for Health, Sprim Brasil, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, Pulse Canada, and GI Foundation. He has *ad hoc* consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the American Society for Nutrition (ASN). He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI), North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada.

AL Jenkins is vice president and partial owner of Glycemic Index Laboratories, Inc. (Toronto, ON, Canada) a clinical research organization. No other authors declared conflict of interest.

Acknowledgments

The authors would like to thank BTGin for donation of the Rg3-enriched KRG (OKBT), Canadian Phytopharmaceuticals for extraction of AG and Roger Foods Ltd. for their donation of the wheat bran. We thank all the participants, investigators, and trial-site staff who were involved in this study. In addition, we thank Dr. Kristina Blaslov for data collection at the Zagreb site.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2019.11.005.

References

[1] Zafari N, Asgari S, Lotfaliany M, Hadaegh A, Azizi F, Hadaegh F. Impact of hypertension versus diabetes on cardiovascular and all-cause mortality in Iranian older adults: results of 14 Years of follow-up. Sci Rep 2017 Oct 27;7(1):14220.

[2] Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison HC, DePalma SM, Gidding S, Jamerson KA, Jones D, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical Practice guidelines. Hypertension 2017 Nov 13.

[3] Prasad K, Sharma V, Lackore K, Jenkins SM, Prasad A, Sood A. Use of complementary therapies in cardiovascular disease. Am J Cardiol 2013 Feb 1;111(3):339–45.

[4] Vuksan V, Sung MK, Sievenpiper JL, Stavro PM, Jenkins AL, DiBuono M, Lee KS, Leiter LA, Nam KY, Arnason JT, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metab Cardiovasc Dis 2008 Jan;18(1):46–56.

[5] Vuksan V, Xu ZZ, Jovanovski E, Jenkins AL, Beljan-Zdravkovic U, Sievenpiper J, Stavro PM, Zurbau A, Duvnjak L, Li MZC. 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, crossover clinical trial. Eur J Nutr 2018.

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

[7] Vuksan V, Stavro MP, Sievenpiper JL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Xu Z. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care 2000 Sep;23(9):1221–6.

[8] Sievenpiper JL, Sung MK, Di BM, Seung-Lee K, Nam KY, Arnason JT, Leiter LA, Vuksan V. Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation- and dose-finding studies. J Am Coll Nutr 2006 Apr;25(2):100–7.

[9] Jeon BH, Kim CS, Park KS, Lee JW, Park JB, Kim KJ, Kim SH, Chang SJ, Nam KY. Effect of Korea red ginseng on the blood pressure in conscious hypertensive rats. Gen Pharmacol 2000 Sep;35(3):135–41.

[10] Jeon BH, Kim CS, Kim HS, Park JB, Nam KY, Chang SJ. Effect of Korean red ginseng on blood pressure and nitric oxide production. Acta Pharmacol Sin 2000 Dec;21(12):1095–100.

[11] Kim ND, Kang SY, Kim MJ, Park JH, Schini-Kerth VB. The ginsenoside Rg3 evokes endothelium-independent relaxation in rat aortic rings: role of K+ channels. Eur J Pharmacol 1999 Feb 12;367(1):51–7.

[12] Jovanovski E, Bateman EA, Bhardwaj J, Fairgrieve C, Mucalo I, Jenkins AL, Vuksan V. Effect of Rg3-enriched Korean red ginseng (Panax ginseng) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. J Am Soc Hypertens 2014 Aug;8(8):537–41.

[13] Stravo PM, Vuksan V. Effect of fermented Korean ginseng fortified with ginsenoside Rg3 on blood pressure in individuals with high normal blood pressure or hypertension. In: Proceedings of the 8th intern symposium on ginseng; Oct28-31 2002. p. 416–23. South Korea.

[14] Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016 Feb 24;352. i717.

[15] Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens 2011 Jul;29(7):1253–69.

[16] Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia 2013 Apr;56(4):686–95.

[17] Pang H, Wang HL, Fu L, Su CY. [Pharmacokinetic studies of 20(R)-ginsenoside RG3 in human volunteers]. Yao Xue Xue Bao 2001 Mar;36(3):170–3.

[18] Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med 2006 Jun 1;354(22):2368–74.

[19] Lee KH, Bae IY, Park SI, Park JD, Lee HG. Antihypertensive effect of Korean Red Ginseng by enrichment of ginsenoside Rg3 and arginine-fructose. J Ginseng Res 2016 Jul;40(3):237–44.

[20] Jeong D, Irfan M, Kim SD, Kim S, Oh JH, Park CK, Kim HK, Rhee MH. Ginsenoside Rg3-enriched red ginseng extract inhibits platelet activation and in vivo thrombus formation. J Ginseng Res 2017 Jan 13.

[21] Nagar H, Choi S, Jung SB, Jeon BH, Kim CS. Rg3-enriched Korean Red Ginseng enhances blood pressure stability in spontaneously hypertensive rats. Integr Med Res 2016 Sep;5(3):223–9.

[22] Ham W, Kim WT, Lee JS, Ju HJ, Kang SJ, Oh JH, Her Y, Chung JY, Park K, Choi YD. Efficacy and safety of red ginseng extract powder in patients with erectile dysfunction. Korean J Urol 2009;50(2):159–64.

[23] Food and Drug Administration. Guidance for industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.

[24] Hong SJ, Fong JC, Hwang JH. Effects of crude drugs on glucose uptake in 3T3-L1 adipocytes. Kaohsiung J Med Sci 2000 Sep;16(9):445–51.

[25] Chung SH, Choi CG, Park SH. Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKAy mice. Arch Pharm Res 2001 Jun;24(3):214–8.

[26] Vuksan V, Sievenpiper J, Xu Z, Beljian-Zdravkovic JA, Arnason J, Bateman R, Leiter L, Josse RG, Francais T, Stavro M. Ginseng and diabetes: a new way to use an old medicine. C J D C 2001;25(2):111–20.

[27] Vuksan V, Sievenpiper JL, Xu Z, Wong EY, Jenkins AL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Stavro MP. Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr 2001 Oct;20(5 Suppl). 370S-80S.

[28] Sen S, Querques MA, Chakrabarti S. North American Ginseng (Panax quinquefolius) prevents hyperglycemia and associated pancreatic abnormalities in diabetes. J Med Food 2013 Jul;16(7):587–92.

[29] Li GD, Lu ZQ. [Effect of ginseng saponins on insulin release from isolated pancreatic islets in the rat]. Zhong Xi Yi Jie He Za Zhi 1987 Jun;7(6):357–9. 326.

[30] Shishtar E, Sievenpiper JL, Djedovic V, Cozma AI, Ha V, Jayalath VH, Jenkins DJ, Meija SB, DeSouza RJ, Jovanovski E, et al. The effect of ginseng (the genus panax) on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. PLoS One 2014;9(9):e107391.

[31] Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. Arch Public Health 2015;73:43.

[32] Catapano AL, Graham I, De BG, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016 Oct 14;37(39):2999–3058.

[33] Gui QF, Xu ZR, Xu KY, Yang YM. The efficacy of ginseng-related therapies in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Medicine (Baltimore) 2016 Feb;95(6):e2584.
[34] Song YB, An YR, Kim SJ, Park HW, Jung JW, Kyung JS, Hwang SY, Kim YS. Lipid metabolic effect of Korean red ginseng extract in mice fed on a high-fat diet. J Sci Food Agric 2012 Jan 30;92(2):388–96.
[35] Kim SH, Park KS. Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol Res 2003 Nov;48(5):511–3.
[36] Mucalo I, Jovanovski E, Vuksan V, Bozikov V, Romic Z, Rahelic D. American ginseng extract (panax quinquefolius L.) is safe in long-term use in type 2 diabetic patients. Evid Based Complement Alternat Med 2014;2014:969168.
[37] Kim YS, Woo JY, Han CK, Chang IM. Safety analysis of panax ginseng in randomized clinical trials: a systematic review. Medicines 2015 Jun;2(2):106–26.
[38] Aa J, Wang G, Hao H, Huang Q, Lu Y, Yan B, Zha WB, Liu LS, Kang A. Differential regulations of blood pressure and perturbed metabolism by total ginsenosides and conventional antihypertensive agents in spontaneously hypertensive rats. Acta Pharmacol Sin 2010 Aug;31(8):930–7.
[39] Sievenpiper JL, Arnason JT, Vidgen E, Leiter LA, Vuksan V. A systematic quantitative analysis of the literature of the high variability in ginseng (Panax spp.): should ginseng be trusted in diabetes? Diabetes Care 2004 Mar;27(3):839–40.