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RESEARCH ARTICLE

A Randomized, Placebo-controlled, Triple-blind Study to Determine the Effect of Farlong Ginseng Plus™ NotoGinseng Extract on Cholesterol and Blood Pressure

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Abstract: ***Objective*:** This randomized, placebo-controlled, triple-blind study examined the efficacy of 12 weeks of Farlong NotoGinseng™ (FNG) supplementation on LDL-C and blood pressure (BP) in otherwise healthy participants (*n*=95) with normal to mild hypertension and hypercholesterolemia.

***Methods*:** Lipid profile, BP, and endothelial vasodilation parameters were assessed at baseline and weeks 4, 8 and 12. Safety was assessed at the screening and end of the study. The Therapeutic Lifestyle Change (TLC) diet was followed during a 4-week run-in and throughout.

***Results*:** Participants on FNG had a 4.33% reduction in LDL-C at week 8 (p=0.045) and a 1.80% improvement in HDL-C at week 12. Those on placebo had a non-significant 1.37% HDL-C reduction at both weeks 8 and 12. The FNG group showed a 0.94% reduction in systolic (SBP) and a 0.16% reduction in diastolic BP (DBP) at week 12. The placebo group also had 0.5% and 1.24% increases in SBP and DBP, respectively. A total of 17.5% of participants supplemented with FNG had improvements in all three CVD risk factors (LDL-C, HDL-C, and SBP) compared to 5.0% of those on placebo (p=0.040). A greater proportion of participants with borderline high baseline LDL-C had reductions in their CVD risk factors (p=0.037) with FNG. However, participants in the placebo group with similar LDL-C characteristics did not have improvements in either their BP or lipid profile.

***Conclusion*:** FNG was well-tolerated and may have a positive influence on reducing CVD risk by improving BP and lipid profile. Left unaddressed, those with CVD risk factors may progress to a more hypertensive and hypercholesterolemic state.

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1. INTRODUCTION

Cardiovascular disease (CVD) is a major cause of mortality, accounting for over 17 million deaths globally [1]. Approximately 71 million Americans and 85 million Europeans are affected by CVD. Estimates indicate the total annual cost associated with CVD is approximately $400 billion in the United States (US) and €169 billion in the European Union (EU) [2-4]. In the US alone, this is predicted to exceed $1 trillion in the next 15 years [2]. According to the World Health Organization (WHO), the rate of CVD worldwide will increase with the rise in the prevalence of risk factors for CVD, such as high blood pressure (BP), elevated blood sugar, and dyslipidemia.

The WHO estimated that greater than 75% of premature CVD is preventable [5]. Hypercholesterolemia and hypertension are well established modifiable CVD risk factors. Regulation of these risk factors through changes to diet and physical activity have been the primary targets of reducing CVD risk [6-8]. Based on the 2017 BP guidelines, approximately 45.6% of adults in the US have hypertension [9, 10]. The National Cholesterol Education Program (NCEP) identified low-density lipoprotein cholesterol (LDL-C) concentrations <100 mg/dL (2.6 mmol/L) as optimal levels of cholesterol for CVD health [11]. Targeting these modifiable risk factors is a critical priority to reduce the health and economic burden of CVD.

The recommended normal-standard-of-care in the management of both hypercholesterolemia and hypertension is lifestyle modification including diet and exercise approaches prior to the introduction of prescription medication [10, 12,

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13]. The Therapeutic Lifestyle Change (TLC) diet is an established dietary intervention which focuses on reducing saturated fat and cholesterol intake and introduces dietary options to enhance LDL-C lowering and weight reduction [11, 14]. The use of lifestyle modification as standard-of-care is partially based on evidence of varied compliance, efficacy and possible side effects from lipid-lowering and anti-hypertensive medications. Specially for BP, epidemiological data suggests that treating hypertension lowers CVD risk, but clinical trials have not substantiated this prediction, as data from various classes of pharmacological interventions have been inconsistent [15-19]. Further, the use of anti-hypertensive medications has shown low compliance [20], consistent with variation in compliance depending on treatment course [21]. Patients may also face the added burden of side effects associated with some pharmaceutical therapies such as statins beta-blockers and angiotensin converting enzyme (ACE) inhibitors [22-24]. The addition of safe and efficacious nutraceuticals for regulation of BP and lipid levels to lifestyle interventions could be beneficial to individuals with mild to moderate hypertension and hypercholesterolemia.

There are many nutraceuticals that have been shown to have lipid-lowering properties that can be used as part of standard-of-care [25]. Ginseng is a promising dietary supplement to complement lifestyle changes in the modulation of blood lipids and BP levels. The bioactive component of ginseng, ginsenosides (saponins) [26], has been shown to exert angiogenic effects by activating vascular endothelial growth factor and its receptor in downstream signaling pathways [27, 28]. Ginsenoside Rg5, a compound synthesized during the steaming process of ginseng promoted angiogenesis and improved hypertension in animal models without adverse effects in the blood vasculature [29]. Rg5 specifically increased phosphorylation of insulin-like growth factor-1 receptor resulting in stimulation of nitric oxide (NO) pathways to enhance angiogenesis [29]. Compared to other species of ginseng, *P. notoginseng* contains more saponin ginsenoside Rg1, which has been shown to have a strong pro-angiogenic effect [27]. Supplementation with *P. notoginseng* in combination with conventional therapy, including anti-ischemic and vascular protective agents, such as nitroglycerin, aspirin, clopidogrel, beta-blockers, and statin, has been previously shown to decrease serum TC, TG and LDL-C [30]. These studies suggest that ginseng may have beneficial clinical applications in the management of CVD. However, there is a lack of well-controlled, randomized double-blind clinical trials that have evaluated the clinical potential of ginseng in normalizing blood lipids and BP [31].

The objective of this study was to examine the efficacy of Farlong NotoGinseng™ (Farlong Ginseng Plus™ Panax Notoginseng extract, FNG) on LDL-C levels and BP in an otherwise healthy population of participants with normal to mild hypertension and hypercholesterolemia who are eligible for normal-standard-of-care. This study also explored a concept used in evidence-based nutrition that was first developed by Heaney *et al.* [32]. Heaney proposed the importance of following the placebo group in a clinical trial to assess the impact of not treating or supplementing a pre-disease population. This was described as a "shift from proof of efficacy to that of probable harms in the absence of the intervention, in the context of nutritional intervention" [32, 33]. In the current study, the lack of intervention in the placebo group of this study population was compared against FNG supplementation in relation to CVD risk markers and the Framingham 10-year risk for CVD over the course of the 12-week study period.

2. MATERIALS AND METHODS

2.1. Participants

Unconditional approval of this study was made by the Institutional Review Board (IRB Services, Aurora, Ontario, Canada) on September 28, 2016 (Pro 00019125) and by Health Canada on November 22, 2016 (223805). The clinical trial was performed according to the ethical guidelines detailed in the Declaration of Helsinki (2008) and complied with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and Good Clinical Practice Current Step 4 Version, dated June 10, 1996. The trial was registered at Clinicaltrials.gov (NCT04069715).

The design was a randomized, placebo-controlled, triple-blind, parallel study conducted at the KGK Science Inc. clinic site (London, Ontario, Canada) from December 15, 2016, to June 1, 2019. Written informed consent was obtained from all participants prior to any study procedures being initiated.

Participants were male and female between the ages of 18 and 75 years, had a body mass index (BMI) between 23.0 and 32.5 kg/m^2, low-density lipoprotein cholesterol (LDL-C) levels between 2.6 and 3.8 mmol/L, and systolic blood pressure (SBP) between 100 and 140 mmHg. Participants were required to follow the TLC diet, maintain current physical activity patterns, and comply with all study requirements.

Individuals were excluded if they had LDL-C $\geq$ 3.37 mmol/L and were deemed high risk based on the Framingham Risk Score; LDL-C >3.5 mmol/L or if they had TC:HDL-C > 5.0 or hs-CRP > 2 mg/L for males older than 50 and females older than 60, and were deemed intermediate risk based on the Framingham Risk Score; TC:HDL-C > 6.0 and were deemed low risk based on the Framingham Risk Score; followed the TLC diet within 12 weeks of screening; used cholesterol- or blood pressure-lowering health supplements within 1 month of randomization; used cholesterol- or blood pressure-lowering prescription drugs within 6 months of randomization; used systemic antibiotics, corticosteroids, androgens, phenytoin, or hormone replacement therapy unless on a stable dose for at least 3 months that was maintained during the study; used ginseng-based drinks or products; participated in exercise totalling more than 24 km or 4,000 kcal per week; were cognitively impaired and/or unable to give informed consent; or had any other condition which in the medical investigator's opinion may have adversely affected the individual's ability to complete the study or its measures or posed significant risk to the individual.

2.2. Investigational Product

The investigational product (IP), Farlong NotoGinseng™ (FNG) and placebo were provided by Yunan PanLongYun-Hai Pharmaceuticals and Longstar Healthpro Inc. DBA Farlong Pharmaceutical. Farlong NotoGinseng™ capsules contained Farlong Ginseng Plus™ Panax Notoginseng extract with excipients magnesium stearate and gelatin. The placebo contained 0.8 mg of turmeric, 153 mg brown rice flour and the same excipients as FNG™ (46 mg of magnesium stearate). Participants were instructed to take two capsules once per day in the morning, thirty minutes before a meal for 12 weeks. In the event a dose was missed, participants were instructed to take the missed dose as soon as they remembered but were not to exceed two capsules per day.

2.3. Therapeutic Lifestyle Change (TLC) Diet

The TLC diet is a lifestyle approach developed by the Adult Treatment Panel III of the NCEP to reduce the risk of coronary heart disease [11]. Participants were counselled on the TLC diet, by a nutritionist. Modifications were made to the TLC diet and did not require including 10-25 g/d viscous fibers and/or 2 g/d plant stanols/sterols, or soy protein as previously published [34]. Participants were required to follow the diet guidelines during a 4-week run-in period prior to their baseline visit and during the 12-week study period.

The goal of the TLC run-in period was to limit confounding due to diet changes and to decrease the placebo effect. All participants were asked to maintain their current level of physical activity during the study.

2.4. Randomization and blinding

Participants were identified by their initials and date of birth and assigned a participant number at their screening visit. Eligible participants were assigned a randomization number by a blinded investigator per the order of the randomization list (www.randomization.com).

In order to maintain concealment allocation, IP and placebo were similar in size, color, taste and texture, were in identical sealed bottles and labelled per the ICH-GCP requirements and applicable local regulatory guidelines. Unblinded personnel who were not involved in any study assessments labelled the IP. Investigators, statisticians, other site personnel and participants were blinded to the products.

2.5. Compliance

Product compliance was calculated by determining the number of dosage units taken divided by the number of dosage units expected to be taken, multiplied by 100. In the event of a discrepancy between the information in the study diary and the amount of study product returned, compliance was based on the product returned unless an explanation for the loss was provided.

2.6. Outcome evaluation

The effect of FNG on change of LDL-C, triglycerides (T-G), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), BP, and endothelial vasodilation was assessed at 8 and 12 weeks of supplementation. The lipid markers were analyzed by a central laboratory using Roche Cobas c701 (LifeLabs, London, ON). Blood pressure was determined from 3 measurements taken 1 minute apart. The same arm was used consistently throughout the study. The EndoPAT (peripheral arterial tone, PAT) measured digital flow-mediated hyperemia in an occluded and control arm. After restricting the occluded arm with a standard BP cuff over the brachial artery for 5 minutes, the surge of blood flow caused an endothelium-dependent flow-mediated dilation, captured by the EndoPAT sensors. A post- to pre-occlusion ratio was calculated by EndoPAT software, providing an index that correlated with endothelial function [35]. Participant's estimated 10-year risk for cardiovascular disease was estimated based on the Framingham Heart Study [36].

Safety outcomes included adverse events (AEs), heart rate, weight, BMI, hematology, and clinical chemistry. Blood samples were obtained *via* venipuncture. Hematology (white blood cell count with differentials, red blood cell count, red blood cell indices, hemoglobin, hematocrit) and clinical chemistry (glycated hemoglobin, electrolytes, bilirubin, alanine aminotransferase, aspartate aminotransferase, estimated glomerular filtration rate, and creatinine) were measured by a central laboratory (LifeLabs, London, ON). Urine pregnancy tests were conducted at the KGK Science Inc. clinic at screening and baseline visits for participants of childbearing potential.

2.7. Study procedures

At the screening visit, participant's medical histories and eligibility were reviewed and the Framingham Risk Score for coronary heart disease was assessed. Blood was collected for hematology, clinical chemistry and serum lipid profile. After eligibility was confirmed, participants received nutrition counselling on the TLC diet. At baseline, participants were randomized to receive a 12-week supply of either FNG or placebo. Baseline and week 4, 8, and 12 visits included a blood lipid panel assessment, an EndoPAT measurement of endothelial vasodilation, and review and documentation of AEs. Study diaries were dispensed at baseline to record daily product use, changes in concomitant therapies, and any adverse events experienced throughout the study.

2.8. Adverse events

Participants recorded any AEs in their daily diary. AEs were classified based on the description, duration, intensity, frequency, and outcome. The Qualified Investigator (QI) assessed all AEs and determined causality and intensity. The Medical Dictionary for Regulatory Activities (MEDRA) terminology version 22.0 was used for coding.

2.9. Statistical analyses

The sample size calculation was based on the primary efficacy outcome of the comparison of the change from baseline at 12 weeks of LDL-C between the FNG and placebo group. Assuming 80% power, significance level of 5%, stan-

dard deviation of 0.60 mmol/L for LDL-C (results from a previous study conducted by KGK Science Inc.) and an estimated 20% attrition over the course of the study, a sample of 100 participants was required (n = 50 per group).

The intent-to-treat (ITT) and safety populations consisted of all participants who was randomized and for whom post-randomization safety information was available. The per protocol (PP) population consisted of all participants who consumed at least 80% of either study product doses, did not have any major protocol violations, and completed all study visits and procedures associated with the primary outcome of serum LDL-C level. Missing values in the ITT and PP populations were imputed with the most recent previously available value. No imputation was performed for missing values of safety variables.

For continuous endpoints measured at baseline, weeks 4, 8, and 12, descriptive statistics (number of participants, mean, standard deviation, median, minimum, maximum) were presented by the intervention group for each visit and for the changes from baseline at each visit. Between-group differences at baseline were assessed by independent two sample t-tests. Satterthwaites test was performed where appropriate. Within-group and between-group differences for changes from baseline were assessed using a mixed model for repeated measures.

Change in estimated 10-year risk for CVD [36] compared to baseline was visualized on a longitudinal scatterplot and linear regression models were fitted with accompanying confidence intervals for both the FNG and placebo groups. A separate analysis was also carried out to evaluate improvements in three risk factors as defined by: decreased LDL-C, increased HDL-C, and decreased SBP compared to baseline. The proportion of participants who improved in all three, at least two, or at least one of these markers compared to baseline were evaluated at weeks 4, 8, and 12. The statistical significance of differences between participants receiving FNG and placebo were evaluated using a one-tailed two-sample Student's t-test. Where sample size was greater than 30 in both groups, parametric tests were used based on convergence of the distribution of means in accordance to the central limit theorem. A post-hoc analysis was carried out on a subgroup of PP participants with baseline LDL-C levels that were >3.5 mmol/L to examine changes in CVD risk factors.

A P-value ≤ 0.05 was considered statistically significant. All statistical analyses were completed using SAS 9.4 for Microsoft Windows [37] or R (version 4.0.2). Unless otherwise specified, all statistical analyses were two-tailed.

3. RESULTS

A total of 384 volunteers were screened and 95 eligible participants were enrolled, with 47 participants randomized to the FNG group and 48 to the placebo group (Fig. **1**).

Forty-two and 43 participants in the FNG and placebo group completed the study, respectively. Overall compliance for both groups was >93%. The results presented are from the PP population. Participant demographic and lifestyle characteristics are presented in (Table **1**). Participant demographics, anthropometrics, and vitals were similar between both groups.

3.1. Efficacy of FNG on serum LDL-C levels

There were no significant differences in serum LDL-C levels between participants supplemented with FNG or placebo at 8 and 12 weeks (Fig. **2**). Participants in the FNG group had a 4.02% reduction in LDL-C at 8 weeks over placebo although this did not reach statistical significance.

Participants supplemented with FNG had a significant 4.33% reduction in LDL-C levels from baseline at week 8 (p=0.045). Although not statistically significant, participants on placebo had a 0.31% increase from baseline in LDL-C levels at week 8. There was no difference from baseline at week 12 for participants in the FNG or placebo group.

3.2. Efficacy of FNG on serum lipid profile

There were no significant differences in serum TG or TC levels at 8 and 12 weeks between participants on FNG or placebo (Supplementary Table **2**).

Although not statistically significant, positive clinically important improvements were seen in other lipid risk markers when assessing within-group improvements. Participants in the FNG group had a 1.80% improvement in HDL-C levels as well as a reduction in TC/HDL-C ratio from baseline at week 12 while those in the placebo group had a 1.37% reduction in HDL-C from baseline at weeks 8 and 12 (Supplementary Table 2).

3.3. Efficacy of FNG on blood pressure

Systolic and diastolic blood pressure measurements at 8 and 12 weeks were not significantly different between the FNG and placebo groups (Fig. **3**). Participants in the FNG group had a 0.94% reduction from baseline in SBP and a 0.16% reduction in DBP at week 12. This reduction translated to a decrease of 1.12 mmHg in SBP at week 12 in the FNG group over placebo. Participants on placebo had non-significant 0.5% and 1.24% increases from baseline at week 12 in SBP and DBP, respectively.

3.4. Analysis of CVD risk factors

Improvement in CVD risk factors over time was examined as a reduction in SBP, reduction in LDL-C and an increase in HDL-C. There was a significantly greater proportion of participants with improvements of at least two CVD risk factors from baseline at week 12 in the FNG group compared to placebo (p=0.007) (Table **2**). A total of 17.5% of participants supplemented with FNG had improvements in all three CVD risk factors compared to 5.0% of those on placebo at week 12 (p=0.040). Similar to reductions in individual risk factors for CVD, participants in the FNG had a 0.1% reduction in estimated Framingham Heart Study 10-year risk for CVD [36] from baseline at week 12. While this was not statistically different from placebo, those in the placebo group had no change over time (Fig. **4**).

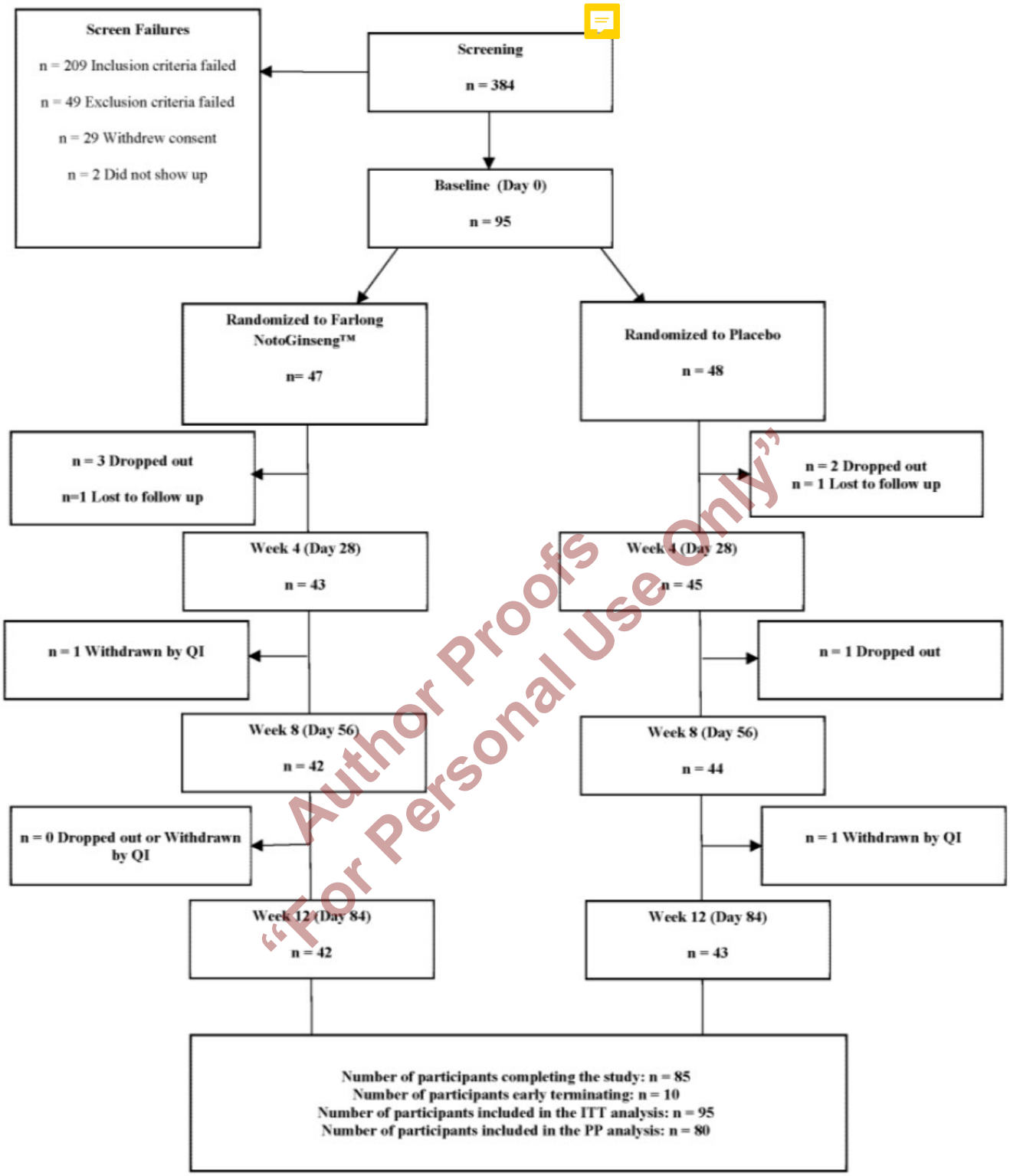

Fig. (1). Disposition of study participants.

Table 1. Baseline demographic and clinical measurements for participants in the per protocol population (*n*=80).

Parameter	FNG (*n*=40)	Placebo (*n*=40)	Between-group *p*-value*
Age (years)	50.68 ± 12.37	49.58 ± 11.49	0.681
Gender [n (%)]			
Female	31 (77.5%)	26 (65.0%)	0.217
Male	9 (22.5%)	14 (35.0%)	
Weight (kg)	77.61 ± 13.17	78.38 ± 11.62	0.781
BMI (kg/m^2)	27.41 ± 2.95	27.86 ± 2.45	0.465
Left Systolic Blood Pressure (mm Hg)	118.95 ± 9.96	117.72 ± 9.84	0.579
Left Diastolic Blood Pressure (mm Hg)	74.65 ± 7.61	74.06 ± 8.83	0.749
Right Systolic Blood Pressure (mm Hg)	119.77 ± 10.80	118.38 ± 11.04	0.575
Right Diastolic Blood Pressure (mm Hg)	75.93 ± 7.67	75.34 ± 8.14	0.740
Heart Rate (bpm)	66.29 ± 9.27	66.33 ± 8.15	0.986
LDL-C (mmol/L)	3.23 ± 0.55	3.23 ± 0.62	0.958
HDL-C mmol/L)	1.64 ± 0.43	1.46 ± 0.30	0.033
Total Cholesterol (mmol/L)	5.39 ± 0.80	5.25 ± 0.74	0.406
Triglyceride (mmol/L)	1.16 ± 0.56	1.25 ± 0.49	0.429

Values are mean ± SD unless otherwise stated.
n, number; SD, standard deviation; Min, minimum; Max, maximum.
*For continuous parameters, the between-group p-value was generated by a two-sample t-test, Satterthwaite test was performed where appropriate.
*For categorical parameters, between-group p-values were generated by Chi-square or Fisher's Exact (2-tail) tests as appropriate.

Table 2. Proportion of participants supplemented with Farlong NotoGinseng™ (FNG) or placebo who had changes in cardiovascular disease risk factors as assessed by improvements in lipid profile (reductions in LDL-C and increases in HDL-C) and reductions in systolic blood pressure, compared to baseline (Week 0) in the per protocol population.

Week	CVD Risk Factors Improved								
	All 3			At Least 2			At Least 1		
	FNG (*n*=40)	Placebo (*n*=40)	*p*-value	FNG (*n*=40)	Placebo (*n*=40)	*p*-value	FNG (*n*=40)	Placebo (*n*=40)	*p*-value
4	7.5%	10.0%	0.351	47.5%	60.0%	0.134	92.5%	87.5%	0.233
8	15.0%	7.5%	0.148	50.0%	55.0%	0.330	97.5%	82.5%	0.014
12	17.5%	5.0%	0.040	67.5%	40.0%	0.007	87.5%	87.5%	0.500

n, number; SD, standard deviation; Min, minimum; Max, maximum.
Statistical significance between participants in FNG and placebo was tested using one-sampled Student's t-test.

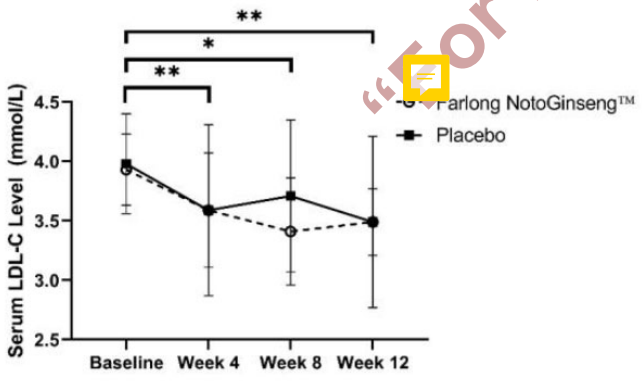

Fig. (2). Serum LDL-C levels for participants supplemented with Farlong NotoGinseng™ (FNG) or placebo in the per protocol population (*n* = 80). ** indicates a significant within-group difference in the FNG group (*p*=0.045).

A post-hoc subgroup analysis identified participants with baseline LDL-C > 3.5 mmol/L. Similar to the PP population, a significantly greater proportion of participants supplemented with FNG had reductions in all three CVD risk factors mentioned above compared to those on placebo (*p*=0.037). At 12 weeks, 41.7% of the participants in the FNG group with baseline LDL-C >3.5 mmol/L had reductions from baseline in their SBP and LDL-C and improvements in HDL-C levels. There were no participants on placebo in this subgroup who showed similar beneficial changes in LDL-C, HDL-C and SBP at weeks 8 and 12.

3.5. Efficacy of FNG on Endothelial Function

There were no significant differences between participants on FNG *vs.* placebo in endothelial function as assessed by reactive hyperemia index (RHI), Augmentation Index (AI) or AI at 75 bpm at 8 and 12 weeks (data not shown).

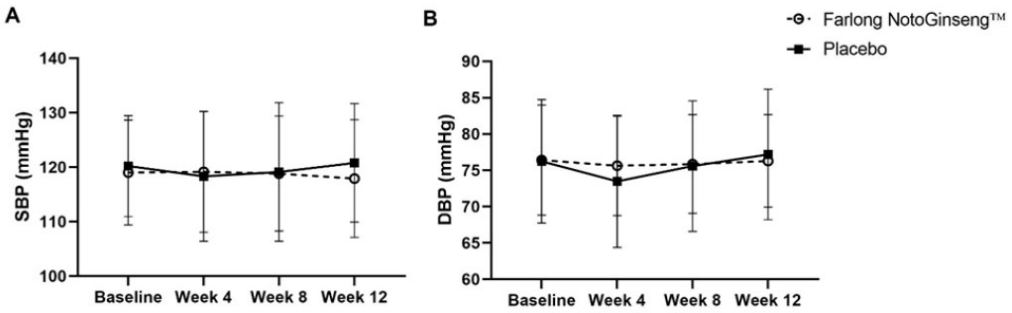

Fig. (3). (**A**) Systolic blood pressure (SBP) and (**B**) diastolic blood pressure (DBP) for participants supplemented with Farlong NotoGinseng™ (FNG) or placebo in the per protocol population (n = 80).

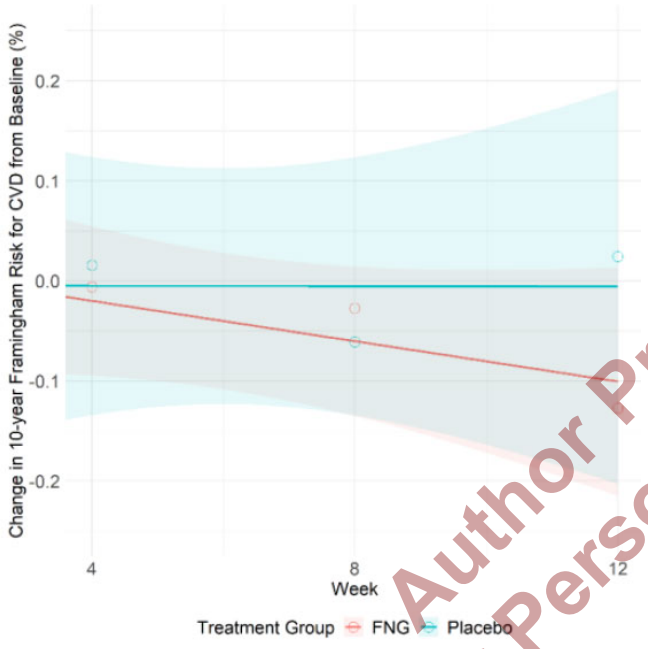

Fig. (4). Change in estimated Framingham Heart Study 10-year risk for cardiovascular disease compared to baseline for participants supplemented with Farlong NotoGinseng™ (FNG) or placebo in the per protocol population (n = 80).

3.6. Safety Evaluation of FNG Supplementation

There were no differences in the number of AEs reported by participants in the FNG or the placebo group or the number of AEs categorized as possibly related to the investigational product or placebo.

A total of 61 post-emergent AEs were reported in this study. Of these, 35 were reported by 23 participants in the FNG group and 26 by 20 participants in the placebo group. Of the 35 AEs in the FNG group, none were classified as most probably related to the investigational product and only one report each of mild gas and bitter taste classified as probably related to the IP which resolved by the end of study. A total of 21 AEs were reported by participants in the placebo group. Of these five were classified as possibly related to the IP and the rest were classified as unlikely related. All AEs were resolved by the end of the study with the exception of one each of a toothache in the FNG group and a headache and psoriasis flare-up in the placebo group. These three AEs were deemed unlikely or not related to the IP.

Hematology, clinical chemistry, electrolytes, and liver and kidney function markers remained within healthy clinical reference ranges in both groups (data not shown). All markers out of laboratory range were deemed not clinically significant and participants were determined to be healthy by the QI based on these values. There were no significant differences in vital signs or anthropometric measurements between the FNG and placebo groups (data not shown).

4. DISCUSSION

Farlong NotoGinseng™ is a highly concentrated *P. notoginseng* extract, and *in vivo* and *in vitro* studies have shown that FNG promoted angiogenesis and improved hypertension [29]. In this randomized, placebo-controlled study, participants supplemented with FNG in combination with the TLC diet showed a significant 4.33% reduction in LDL-C from baseline at week 8, although not statistically significant. Similarly, at 12 weeks, although not statistically significant, clinically relevant improvements were seen in the lipid profile, marked by reductions in LDL-C and increases in HDL-C accompanied by improvements in SBP and DBP. Participants on placebo had reductions in HDL-C and increases in SBP and DBP after 12 weeks. Collectively, a significantly greater number of participants supplemented with FNG had improvements in two or more CVD risk factors (decreased LDL-C and SBP and increased HDL-C) compared to placebo at week 12.

This study enrolled participants deemed healthy but had LDL-C levels that were above the optimal level of <2.6 mmol/L, increasing their risk of CVD [11]. They did not have LDL-C levels that were borderline to very high. These participants were not on any prescribed medications for the treatment of hypercholesterolemia or hypertension and were eligible for lifestyle modification, recommended in normal standard-of-care. The lack of an intervention in a population at risk of CVD, represented by the placebo group resulted in a negative impact on cardiovascular risk factors. The find-

ings in the placebo group support a concept by Heaney *et al.* that is used in the development of nutrient evidence where the authors suggest that the lack of an intervention should be considered and a shift be made from proof of efficacy to that of probable harm in the absence of an intervention [32], [33]. Heaney suggests the importance of assessing the balance between potential harm of making recommendations and the potential harm of not making it in terms of evidence-based nutrition [33]. This concept and the challenges of determining clinical efficacy of dietary supplements and CVD have more recently been discussed [38]. This concept has been observed in other studies with populations with higher than optimal LDL-C levels based on NCEP guidelines [34] and in participants with mildly elevated BP [39]. Therefore it is noteworthy that participants in the placebo group had a 1.37% reduction in HDL-C at 8 and 12 weeks as well an increase in SBP from baseline at week 12. While the TLC diet helps in mitigating the impact of negative changes in the lipid profile it's effects may be limited and support short term changes and previous literature [40, 41]. However in the absence of intervention, the progression to a pre-disease and perhaps further to a disease state may be inevitable for some of the participants. The placebo group in the current study is a possible pre-disease population where in the absence of intervention may progress to disease over time.

The negative impact of a lack of intervention is further illustrated by analysis of reduction in CVD risk factors over time between FNG and placebo. When examining improvements in all three CVD risk factors (LDL-C, HDL-C and SBP), there were only 5.0% of participants on placebo that had improvements compared to 17.5% of those supplemented with FNG. Further, as identified in (Table **2**), there was an increasing proportion of participants with improvements in individual CVD risk factors with FNG supplementation compared to placebo. This translated into no change in estimated Framingham 10-year risk for CVD [36]at week 12, whereas those in the FNG group had a 0.1% reduction in 10-year risk for CVD from baseline at week 12. It is likely that a greater division between placebo and FNG groups in terms of 10-year CVD risk would be observed with a longer supplementation period. The lack of response observed in the placebo group demonstrates the possibility that in this population, the absence of intervention and left untreated, there may be detrimental effects on cardiovascular health. Thus the consideration of the concept of the prevention of probable harm is seen when focusing on the negative trajectory of the results in the placebo group as evidenced in this study and others [34, 39].

While the week 12 improvements in lipid profile and BP with FNG supplementation were not statistically significant, there is clinical relevance in improving these risk factors. When combined with the TLC diet, participants supplemented with FNG for 12 weeks had a 5% greater reduction in LDL-C than those on placebo. A 1% reduction in LDL-C equates to a 1% reduction in risk of heart disease [42]. Moreover, HDL-C increased by 1.8% from baseline at week 12 week in the FNG group and a 1% increase in HDL-C is associated with a 2-3% decrease in CVD risk [42]. Improvement in lipid profile, marked by a reduction in LDL-C and increase in HDL-C, is consistent with athero-protection and associated with reduced risk of CVD [43]. The increase in HDL-C also led to a decrease in the ratio of TC to HDL-C, a known predictor of cardiovascular risk. Reductions in this ratio are cardioprotective [44]. In addition to changes in lipid profile, after 12 weeks of supplementation, there was a reduction in both SBP and DBP in the FNG Group, whereas increases occurred for participants on placebo. The 1.12 mmHg improvement in SBP seen in the FNG group is approaching clinical relevance as reductions in BP as little as 2 mmHg is associated with lower risk of cardiovascular events [45, 46]. It is noteworthy that these changes or trends observed in this study were in a population with sub-optimal levels of LDL-C and were not taking any lipid lowering medication. Therefore to see changes in this population presents room for application of FNG to a population at greater disease risk for the prevention of movement into a severe disease phenotype.

In a post-hoc subgroup analysis, there was a significantly greater proportion of participants supplemented with FNG with borderline high LDL-C (>3.5mmol/L) at baseline that had beneficial improvements in lipid profile and SBP, compared to placebo. Taking these risk factors together, the modest improvements in lipid profile and BP could potentially translate to a reduction in CVD risk. Risk factors for CVD frequently co-exist, approximately 80% of patients from the Framingham Heart study with hypertension presented with additional CVD risk factors [47]. The combination of hypercholesterolemia and hypertension more than additively increases the risk of CVD compared to one risk factor alone [48]. Therefore, the efficacy of FNG in improving lipid profile and SBP in 41.7% of participants with borderline high LDL-C levels may be clinically relevant in terms of CVD risk and warrants further investigation in a study with a larger sample size. Further, it is possible that with a longer study duration, there may have been a greater proportion of participants with improvements in CVD risk factors including BP. Previous studies examining the efficacy diet and exercise for preliminary treatment of hypercholesterolemia [34, 41] and cardiovascular disease risk [49] reported intervention lengths up to 18 months. Future studies with FNG supplementation should consider a longer study duration to examine the efficacy of FNG supplementation on lipid and BP markers.

No safety concerns were raised in this study and evaluation of safety parameters demonstrated that FNG was well tolerated. There were no serious adverse events during the study and only 1 gastrointestinal adverse event of mild gas was deemed to be probably related to FNG. There were no significant differences in hematology and clinical chemistry parameters as well as vitals and BMI between participants supplemented with FNG compared to placebo, and all values remained within healthy clinical range. The placebo consisted of 0.8 mg of turmeric, 153 mg of brown rice flour and 46 mg of magnesium stearate. To ensure blinding allocation concealment tumeric was included as a colorant to aid in the

masking between the products. This ingredient is commonly used for this purpose in both conventional foods and nutraceuticals. With only 0.8 mg of turmeric, the quantity of active components (curcuminoids) is very low, approximately 16 - 72 µg, assuming 2-9% curcuminoids [50]. As curcuminoids have limited absorption at high doses [51], no effect of turmeric on metabolism and health is expected. Brown rice flour is commonly used as inert filler as it has a neutral taste, low energy and fiber content and is hypoallergenic [52]. Therefore, it was deemed appropriate for this study and was not expected to have an effect on the outcomes of interest [52]. Both the placebo and IP contained magnesium stearate. This ingredient is one of the most common excipients used in foods and nutraceuticals [53]. In this study, magnesium stearate was used as a glidant or flow-enhancing agent for the powder.

CONCLUSION

In conclusion, a significantly greater number of participants supplemented with Farlong NotoGinseng™ had reductions in three CVD risk factors (LDL-C, HDL-C and SBP) compared to placebo a population with cholesterol levels above optimal. Participants supplemented with FNG had significant reductions in serum LDL-C from baseline at 8 weeks which was maintained to 12 weeks. Forty-two percent of participants with borderline high levels of LDL-C at baseline had reductions in CVD risk factors when supplemented with FNG. It is possible that if left unaddressed, these participants may progress to a more hypertensive and hypercholesterolemic state, thereby increasing CVD risk. The findings of this study demonstrate that FNG supplementation was well tolerated and may have a positive influence on reducing the risk of CVD by decreasing BP and improving lipid profile towards a less atherogenic phenotype.

LIST OF ABBREVIATIONS

ACE = Angiotensin Converting Enzyme
AE = Adverse Event
AI = Augmentation Index
BMI = Body Mass Index
BP = Blood Pressure
CVD = Cardiovascular Disease
EU = European Union
FNG = Farlong NotoGinseng™
HDL-C = High-density Lipoprotein Cholesterol
ICH = International Council for Harmonization
IP = Investigational Product
ITT = Intent-To-Treat
LDL-C = Low-density Lipoprotein Cholesterol
MEDRA = Medical Dictionary for Regulatory Activities
NCEP = National Cholesterol Education Program
NO = Nitric Oxide
PAT = Peripheral Arterial Tone
PP = Per Protocol
QI = Qualified Investigator
RHI = Reactive Hyperemia Index
TC = Total Cholesterol
TG = Triglyceride
TLC = Therapeutic Lifestyle Change
US = United States
WHO = World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board (IRB Services, Aurora, Ontario, Canada) on September 28, 2016 (Pro 00019125) and by Health Canada on November 22, 2016 (223805).

HUMAN RIGHTS

No animals were involved in this study. The clinical trial was performed according to the ethical guidelines detailed in the Declaration of Helsinki (2008) and complied with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and Good Clinical Practice Current Step 4 Version, dated June 10, 1996.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants prior to any study procedures being initiated.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analysed during the current study are available from the corresponding author [M.E.] on reasonable request.

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CONFLICT OF INTEREST

JS and AZ are employees of Farlong Pharmaceutical.

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SUPPORTIVE/SUPPLEMENTARY MATERIAL

Table S1: CONSORT 2010 checklist of information to include when reporting a randomised trial.

Table S2: Serum lipid profile for participants supplemented with Farlong NotoGinseng™ (FNG) or placebo in the per-protocol population (*n*=80).

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