The Effects of *Panax* Ginseng on Lipid Profile, Pro-oxidant: Antioxidant Status and High-sensitivity C Reactive Protein Levels in Hyperlipidemic Patients in Iran

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ABSTRACT

Background: Because of the conflicting results from previous studies regarding the efficacy of *ginseng* on lipid profile and anti-inflammatory and anti-proliferative activities of its components, we aimed to evaluate the effects of *Panax ginseng* on lipid profile, pro-oxidant – anti-oxidant status and high-sensitivity C reactive protein (hs-CRP) levels.

Methods: Forty Iranian hyperlipidemic patients were randomly assigned to placebo ($n = 20$) or control ($n = 20$) groups in this double-blind randomized controlled trial. The *ginseng* or placebo was taken two capsules twice a day for 8 weeks. Total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting blood glucose, serum creatinine and hs-CRP levels and pro-oxidant – anti-oxidant balance (PAB) were estimated before and after intervention.

Results: There were no significant differences between the two groups with respect to changes in serum TG, LDL-C, HDL-C, and TC/HDL-C levels. Nor were there significant differences between the two groups with respect to changes in hs-CRP level and PAB from baseline to week 8.

Conclusions: Our study demonstrates that *ginseng* does not have significant effects on lipid profile, Hs-CRP level and PAB. Further clinical studies, with a larger sample size, more prolonged period of therapy are needed to investigate the therapeutic effects of *ginseng*.

Keywords: High sensitivity C reactive protein, lipid profile, *Panax* ginseng, pro-oxidant – anti-oxidant status

INTRODUCTION

Panax ginseng is an important medicinal plant cultivated largely in Korea. The mature roots of these plants are used in many traditional medical formulations to treat several different conditions.[1] It has been used for more than 2000 years in Asia as a traditional medicine and dietary supplement.[2]

The primary active constituents of *ginseng* are thought to be the ginsenosides, which include more than 20 saponin triterpenes

similar in structure to steroid hormones. These are believed to act via hormone receptors in the hypothalamus, pituitary glands, and other hormone sensitive tissues. Ginsenosides stimulate secretion of adrenocorticotropic hormone, leading to production of increased release of adrenal hormones, including cortisol. Ginsenosides have also been reported to stimulate ribonucleic acid (RNA) transcription, protein synthesis, and hepatic cholesterol production. In addition, they may stimulate synthesis of adrenal hormone precursors.[3,4]

According to recent studies, a hypolipidemic effect of *Panax ginseng* extract (PGE) is associated with decrease in total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), Muscular Dystrophy Association (MDA) levels and an increase in high-density lipoprotein (HDL) level. Administration of PGE increased serum superoxide dismutase (SOD) and catalase (CAT) activities while decreased MDA level indicating that antioxidant potential of PGE might induce hypolipidemic effect as one of action mechanism.[4]

Evidence suggests that *P. ginseng* lowers cortisol levels in individuals with diabetes, while increasing cortisol levels in non-diabetic individuals.[3,4]

Specific triterpenoid saponins (diols) are claimed to cause improvements in endurance and learning. These compounds are also believed to contribute to sedative and antihypertensive properties. A second group (trials) has been reported to increases blood pressure and function as central nervous system stimulants. Ginsenosides have carbohydrate-sparing actions and may increase muscle endurance.[3,4]

The effects of *P. ginseng* have been reported to be dose-dependent. Low-doses increase blood pressure, while high doses exhibit a hypotensive effect.[3,4] Additionally, *P. ginseng* is reported to have immunostimulatory effects on the reticuloendothelial system. *P. ginseng* has also been reported to reduce weight loss and stabilize white blood cell counts during chemotherapy and to accelerate postsurgical recovery. *P. ginseng* helps the body adapt to stresses caused by chemotherapy and radiation.[3,4]

Many reports from clinical and experimental studies suggested that *ginseng* may have beneficial effects on reducing serum TC level and enhancing antioxidant status.[5,6]

However, Ismail *et al*. reported that a *ginseng* extract (G-115) had no significant hypolipidemic or antioxidant effects in rabbits.[7]

Administration of *P. ginseng* has minimal side effects.[8,9]

Ginsenosides, have been known for the anti-inflammatory and anti-proliferative activities by significant inhibitory effect on tumor necrosis factor-alpha.[10]

The most extensively studied biomarker of inflammation in cardiovascular diseases is C-reactive protein (CRP), for which standardized high-sensitivity assays (hs-CRP) are widely available.[11,12]

According to conflicting results from previous studies regarding the efficacy of *ginseng* on lipid profile and anti-inflammatory and anti-proliferative activities of its components, we aimed to evaluate the effects of *P. ginseng* on lipid profile, pro-oxidant – anti-oxidant status and hs-CRP level.

METHODS

This study was conducted as a double-blind randomized controlled trial. For the proposed study, to achieve a similar difference between the *ginseng* extract and placebo treatment groups with an 80% power and confidence interval of 95%, it is estimated that a sample size of 15 subjects per group will be required, that is, 30 in total. 40 patients were selected. The sample size was calculated according to the previous study of Kim, *et al*.[13] These patients referred to the cardiology clinic at Ghaem Hospital, Mashhad, Iran. No patients were on treatment with any medications. The inclusion and exclusion criteria were defined according to The American College of Cardiology (ACC) /The American Heart Association (AHA) guidelines. The inclusion criteria were: (1) Serum LDL-cholesterol (LDL-C) level 160-190 mg/dl in patients with 0-1 cardiovascular risk factors, (2) Serum LDL-C level 130-160 mg/dl in patients with >1 cardiovascular risk factors and <10% coronary heart disease (CHD) risk at 10 years according to Framingham risk scores, (3) Serum LDL-C level 100-130 mg/dl in patients with CHD equivalent risk factors and >20% CHD risk at 10 years according to Framingham risk scores, (4) TG level <200 mg/dl, (5) age >20 years.

The exclusion criteria were: (1) Overt hyperlipidemia requiring medical treatment (Serum LDL-C level >190 mg/dl, TG

level <200 mg/dl); (2) past history of diabetes mellitus or fasting blood glucose level >126 mg/dl; (3) past history of documented cardiovascular disease; (4) pregnancy and lactation; (5) past history of renal failure or glomerular filtration rate <60 mL/min; (6) Acute infection, (7) Active bleeding with the exception of menses, (8) Taking anticoagulant; (9) psychosis or anxiety disorder; (10) mono amino oxidase inhibitors.

Of the total of 40 patients recruited and randomized to group, 20 participants were assigned to the placebo group, and 20 to the *ginseng* group. Patients visited the clinic over a period of 8 weeks at three stages (0, 1, and 2). At each clinic visit, height, weight, and body mass index (BMI) were measured for each participant. After allowing participants to rest for a minimum of 10 min, systolic and diastolic blood pressures were measured twice, and the averages were obtained. At stages 0 and 2, blood sampling and biochemical evaluation were undertaken. At stages 0 and 1, patients were administered the drug, or placebo [Figure 1]. For all the patients, we recommended the same diet according to ACC/AHA guidelines before intervention. Cardiac examinations also were done for all patients each stage. Patients were matched for confounding factors in both groups.

Blood sampling was obtained before and after the 8 weeks' drug/placebo administration. We choose an 8 week period according to the previous study of Kim *et al*.[4] After 12 h of fasting 10 mL of blood was collected from each patient.

Out of 10 mL, 5 mL of blood was collected into
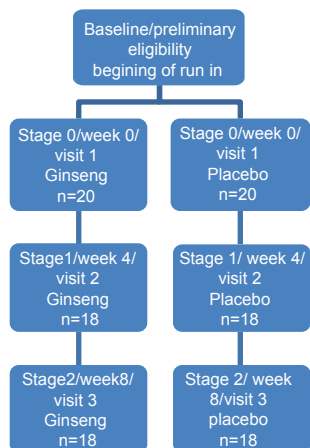
Figure 1: Study design and patient allocation design chart

chilled tubes containing citrate and the rest into plain chilled tubes to obtain serum. Samples were centrifuged. Then, serum and plasma were frozen in dry ice prior to being stored at −80°C.

Blood samples were used for estimation of TC, TG, LDL-C, HDL-cholesterol (HDL-C), fasting blood glucose, serum creatinine and hs-CRP.

Pro-oxidants-anti-oxidants balance (PAB) assay was performed according to Alamdari DH *et al*. method.[14]

The standard solutions were prepared by mixing varying proportions (0-100%) of 1 mM hydrogen peroxide with 6 mM uric acid (in 10 mM NaOH).

The following standard solutions were prepared separately: Vitamin C (0-800 μM), Trolox (0-800 μM), uric acid (0-6 mM in 10 mM NaOH), glutathione (0-2500 μM), albumin (0-1000 mM [68 g/L]), hydrogen peroxide (0-1000 μM) and tert-buthylhydroperoxide (0-1000 μM).

Tetramethylbenzidine (TMB) solution was prepared by dissolving one TMB tablet in 10 mL of substrate buffer (0.05 mM phosphate citrate buffer, pH 5). For preparation of TMB cation, 18 μL of fresh chloramine T (10 mM) solution was added to 1 mL of TMB solution, incubated for 20 min; and 1.25 U of peroxidase enzyme solution was added to 9 mL of TMB solution. The working solution was prepared by mixing the two latter solutions, incubated for 5 min at room temperature and used immediately; 10 μL of each sample, standard or blank (distilled water) was mixed with 200 μL of working solution, in each well of a 96-well plate, which was then incubated in a dark place for 12 min at room temperature; at the end of the incubation time, 100 μL of 2N HCl was added to each well. The plate was then incubated for 45 min in a dark place and measured in an ELISA reader at 450 nm with a reference wavelength of 620 nm or 570 nm. A standard curve was provided from the values relative to the standard samples. The values of the PAB are expressed in arbitrary units, which are the percentage of hydrogen peroxide in the standard solution multiplied by 6. The values of the unknown samples were then calculated based on the values obtained from the above standard curve.

TC, TGs and HDL-C were measured using a standard enzymatic method by Biosystem kits and using an auto analyzer (BT 3000 model). LDL-C was calculated by Friedwald equation: LDL-C = TC − (TG/5 + HDL-C).

We measured hs-CRP using polyclonal antibodies against CRP coated onto latex participles. We measured it by Biosystem commercial kit with auto analyzer BT3000.

We measured FBS and serum creatinine using standard methods by Biosystem commercial kit with auto analyzer BT3000.

Ginseng extract was supplied by Gol Daru Co. Ltd., Tehran, Iran. *Ginseng* extract was provided as soft capsules. Each capsule contained 250 mg of *ginseng* extract, that contained 7 mg of ginsenosides and the components were characterized as follows: 2-3% for ginsenosides (Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1), panacene, beta sitosterol, low molecular weight polysaccharides, flavonoids. Ginsenosides or panaxosides are a class of steroid glycosides, and triterpene saponins, found exclusively in the plant genus *Panax ginseng*. Rb1 appears to be most abundant in *Panax quinquefolius* (American *ginseng*). Ginsenoside-Rc is a steroid molecule that can be found in the *ginseng* plant and is recognized for producing more sedative related results than other ginsenosides, such as ginsenoside-Re or ginsenoside-Rg. Rg1 appears to be most abundant in *P. ginseng* (Chinese/Korean *ginseng*).

The active (*ginseng*) group took two capsules twice a day for 8 weeks. The placebo was prepared in an industrial laboratory of the School of Pharmacy at Masshad University Medical School. We used a Granular powder included Lactose (66%), starch (33%) and Magnesium stearate (1%) as a placebo. The placebo was also taken twice a day for 8 weeks.

Statistical analysis was performed using SPSS version 16.0 for Windows. All data were presented as mean ± SD.

An independent *t* test was used to compare changes from baseline to 8 weeks between the two groups. In addition, a paired *t* test was used to compare baseline data with changes at 8 weeks for each group. The repeated measure ANOVA test was used to compare quantitative variables. Mann-Whitney and Chi-squared tests were used to compare ordinal and nominal qualitative variables, respectively. *P* <0.05 was considered significant for all data analyses.

The study, which was conducted according to the declaration of Helsinki, was approved by the Mashhad University of Medical Sciences Ethics Committee and all participants gave written informed consent.

Two participants in the control and one participant in the case group dropped out of the study because of failure to follow the protocol. One patient in the case group dropped out of study due to abnormal liver function test results. This did not have effect the power of the study substantially because we overestimate the sample size.

RESULTS

There was no significant difference between the two groups with respect to the occurrence of side effects (loss of appetite, diarrhea, headache, blurred vision, insomnia, agitation, rashes and bleeding).

Table 1, shows the changes in BMI, creatinine, and fasting blood sugar from baseline to week 8 [Table 1].

At the beginning of the study, there was no significant difference between the two groups regarding TC level. After 8 weeks of treatment, the serum TC level in the *ginseng* group decreased from 225.62 ± 44.41 mg/L to 184.8 ± 25.9 mg/L (*P* < 0.0001). However, there was no significant difference between the two groups with respect to the change in serum TC level [Table 2].

Table 1: Changes in body mass index, creatinine, fasting blood sugar from baseline to week 8

	Placebo group (*n*=18), mean±SD	*P*a	*Ginseng* group (*n*=18), mean±SD	*P*a	*P*b
BMI, kg/m^2	Baseline: 29.3±3.3	ns	Baseline: 27.6±3.2	ns	ns
	Week 8:29.1±3.3		Week 8: 27.5±3.2		
creatinine, mg/dl	Baseline: 0.99±0.19	ns	Baseline: 0.9±0.13	ns	*n*
	Week 8: 0.92±0.16		Week 8: 0.89±0.12		
FBS, mg/dl	Baseline: 83.9±22.2	ns	Baseline: 82±13.47	ns	ns
	Week 8: 94±27.1		Week 8: 89.06±12.35		

Data are presented as mean±SD, BMI=Body mass index, Cr=Plasma creatinine concentration, FBS=Fasting blood sugar, ns=Non-significant, aPaired *t* test comparing mean at baseline with mean at week 8 by group, bIndependent *t* test comparing supplementation effects between two groups

There were no significant differences between the two groups regarding TG, LDL-C, HDL-C, TC/HDL-C levels, at the beginning of study. After 8 weeks of treatment, the serum TG, LDL-C, HDL-C, TC/HDL-C levels in the *ginseng* group decreased from 147.31 ± 93.54 mg/L, 152.53 ± 41.33 mg/L, 43.6.7 ± 9.97 mg/L, 5.33 ± 38.91.15 mg/L to 93.56 ± 30.6 mg/L, 124.78 ± 19.22 mg/L, 41.5 ± 9.77, 4.5 ± 0.64 mg/L ($P < 0.006, 0.0001, 0.173, 0.0001$), respectively. However, there were no significant differences between the two groups with respect to the change in serum TG, LDL-C, HDL-C and TC/HDL-C levels [Table 2].

There were no significant differences between the two groups with respect to changes in serum hs-CRP and PAB from baseline to week 8 [Table 3].

DISCUSSION

Our study was a randomized double blind controlled trial, which aimed to determine the effects of *ginseng* root extract on lipid profile, hs-CRP and PAB.

In the current study, 40 patients were recruited. Three participants dropped out of the study because of failure to follow the regimen. One patient in the *ginseng* group dropped out of study due to abnormal liver function test results.

No major side effects were detected, except the elevation of liver enzymes in one patient. After 1 month, one patient was found to have aminotransferase level more than twice the upper limit of normal. Aminotransferase level became normal after discontinuation of *ginseng* capsules. No previous study has reported this side-effect. Gastrointestinal side-effects were the most prevalent one. Surprisingly, gastrointestinal side-effects were more prevalent in the placebo group, but this was not statistically significant. Placebo contained lactose that could be responsible for gastrointestinal side-effects.

Overall, no statistically significant difference was detected between the case and control groups regarding side-effects.

According to Kim *et al.* study, *ginseng* showed significant effects on weight and fat mass

Table 2: Changes in lipid profiles from baseline to week 8

	Placebo group (*n*=18), mean±SD	P^a	*Ginseng* group (*n*=18), mean±SD	P^a	P^b
TC, mg/dl	Baseline: 234.45±48	0.0001	Baseline: 225.62±44.41	0.0001	ns
	Week 8: 204.5±36.02		Week 8: 184.8±25.9		
TG, mg/dl	Baseline: 140.75±75.45	0.006	Baseline: 147.31±93.54	0.001	ns
	Week 8: 122.7±57.69		Week 8: 93.56±30.6		
LDL-C, mg/dl	Baseline: 161.7±38.9	0.0001	Baseline: 152.53±41.33	0.0001	ns
	Week 8: 138.4±28.97		Week 8: 124.78±19.22		
HDL-C, mg/dl	Baseline: 44.6±10.21	ns	Baseline: 43.62±9.97	ns	ns
	Week 8: 41.5±9.19		Week 8: 41.5±9.77		
TC/HDL-C	Baseline: 5.39±1.21	0.0001	Baseline: 5.33±1.15	0.0001	ns
	Week 8: 5.08±1.1		Week 8: 4.59±0.64		

TC=Total cholesterol, TG=Triglyceride, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, ns=Non-significant. [a]Paired *t* test comparing mean at baseline with mean at week 8 by group, [b]Independent *t* test comparing supplementation effects between two groups

Table 3: Changes in high-sensitivity C-reactive protein, pro-oxidant-anti-oxidant balance from baseline to week 8

	Placebo group (*n*=18), mean±SD	P^a	*Ginseng* group (*n*=18), mean±SD	P^a	P^b
hs-CRP, mg/dl	Baseline: 2.5±0.59	*ns*	Baseline: 2.63±1.85	ns	ns
	Week 8: 2.9±1.51		Week 8: 2.3±1.2		
PAB	Baseline: 79.16±22.8	*ns*	Baseline: 71.12±24.58	ns	ns
	Week 8: 77.43±28.01		Week 8: 76.1±28.01		

hs-CRP=High-sensitivity C-reactive protein, PAB=Pro-oxidant-anti-oxidant balance, ns=Non-significant. [a]Paired *t* test comparing mean at baseline with mean at week 8 by group, [b]Independent t test comparing supplementation effects between two groups

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reduction.[4] However, in our study, administration of *ginseng* had no significant effects on BMI and fat mass during the same period of treatment. This may be due to the greater sample size in our study. In addition, the dosage of PGE in our study was lower than Kim study.

Baseline demographic characteristics, lipid profiles, hs-CRP, creatinine level, fasting blood glucose were not significantly different between the two groups.

In our study, administration of *ginseng* significantly reduced TC, LDL-C, TG, TC/HDL-C levels during the period of study; however, there were no significant difference between the two groups with respect to the same effect.

Previous studies have demonstrated conflicting results regarding efficacy of *ginseng* on lipid profile. Kim *et al.* conducted a study that was not randomized and did not have control group. In this study, administration of *ginseng* at the dose of 8 g/day, reduced lipid levels.[4] In Sotaniemi *et al.* study, TG level decreased and HDL-C level increased after administration of 100-mg and 200-mg doses of *ginseng* but these effects were not statistically significant.[15] The result of this study is consistent with our own study. The sample size and study duration and *ginseng* dosage is similar to that used in our study.

In the study of Zuin *et al.*, administration of a 40-mg dose of *ginseng* twice daily, had no effect on lipid profile.[16] This may due to low dosage of *ginseng* compared to our study. The duration of this study was longer than ours and the sample size was similar to our study.

Experimental and clinical evidences accumulated since 1990 have established inflammatory processes as important contributors to atherogenesis, as well as to the vulnerability of an atherosclerotic lesion to rupture or erosion.[11]

Based upon this evidence, protein markers of inflammation have been studied as non-invasive indicator of underlying atherosclerosis in apparently healthy individuals and of the risk of recurrent events in patients with established atherosclerotic vascular disease. The most extensively studied biomarker of inflammation in cardiovascular diseases is CRP.[9,10] CRP is an acute phase protein that is produced predominantly by hepatocytes under the influence of cytokines such as interleukin-6 and tumor necrosis factor-alpha.[17]

Data from more than 30 epidemiologic studies have shown a significant association between elevated serum or plasma concentrations of CRP and the prevalence of underlying atherosclerosis, the risk of recurrent cardiovascular events among patients with established disease, and the incidence of first cardiovascular events among individuals at risk for atherosclerosis.[18,19]

Ginsenosides, have been known for their anti-inflammatory and anti-proliferative activities by significant inhibitory effect on tumor necrosis factor-alpha, *in vivo*.[10] According to this evidence, we evaluated the correlation between administration of *ginseng* and the level of hs-CRP. Our results showed no significant difference between the case and control group with regard to hs-CRP level.

Previous studies showed a heightened state of oxidative stress following acute coronary syndrome and suggested that the PAB value may be considered as a cardiovascular risk predictor to estimate the extent of oxidative stress.[20,21] In our study, *ginseng* did not improve the PAB.

CONCLUSIONS

Our study demonstrates that *ginseng* does not appear to have any significant effects on lipid profile, hs-CRP level and PAB. We suggest further clinical studies, with greater sample size, more prolonged period of therapy to investigate the therapeutic effects of *ginseng*. The present study had several limitations. First, *ginseng* was administered at a dose of 500 mg/day for a limited period (8 weeks), and longer-term studies are necessary to show that this effect is sustained. Second, using several doses of *ginseng* could have been useful to determine whether the observed effects of *ginseng* are dose-dependent and whether higher doses exert more dramatic effects.

ACKNOWLEDGMENTS

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