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Lipid Lowering Effect of Ginseng and Alpha-Lipoicacid in Hypercholesterolemic Patients

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Abstract: Alpha-lipoic acid and panax ginseng are widely used as natural dietary supplements because these compounds exert antihypercholesterolemic effects, not only in experimental animals but also in humans. The current study aimed to evaluate the effects of supplementation with lipoic acid (LA) and panax ginseng on the lipid profile of newly investigated hypercholesterolemic patients. Forty adult newly investigated hypercholesterolemic patients, ranging in age from 40 to 60 years,were advised to perform exercise one hour daily and to consume low fat diet and divided in to three groups as follows; Group 1 (healthy individuals served as normal control), Group 2 receiving 600 mg alpha-lipoic acid twice daily for two months and Group 3 receiving 100 mg ginseng twice daily for two months. Then plasma lipid profile was determined. Administration of alpha-lipoic acid for one month showed a significant reduction in LDL only, while after two months both low-density lipoprotein and total cholesterol were significantly reduced as compared to hypercholesterolemic patients, on the other hand administration of panax ginseng for one or two months showed a significant reduction in low-density lipoprotein, total cholesterol, LDL/HDL and CHOL/HDL ratios as compared to hypercholesterolemic patients. Although this study showed an improvement in low-density lipoprotein and total cholesterol in newly investigated hypercholesterolemic patients after alpha-lipoic acid administration for two months, the improvement effects of panax ginseng was shown to be more effective in reducing low-density lipoprotein, total cholesterol, LDL/HDL and cholesterol/HDL ratio. The current study concluded that panax ginseng supplement may be useful in improving hyperlipidaemia more than alpha-lipoic acid in newly investigated hypercholesterolemic patients.

Key words: Ginseng · Alpha Lipoic Acid · LDL · CHOL · Hypercholesterolemia

INTRODUCTION

A high-fat diet (HFD) has been reported to adversely affect the health of humans and animal species [1]. The relationship between hypercholesterlemia with the prevalence of cardiovascular diseases has been well documented. Increased in plasma low density lipoprotein concentration has been associated with the susceptibility of developing atherosclerosis [2,3]. In contrast to the adverse effects of an elevation of LDL, the concentration

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of high density lipoprotein (HDL) correlates inversely with atherosclerosis development [3, 4].The current Adult Treatment Panel (ATP III) guidelines have designated LDL cholesterol as the major target for the treatment of dyslipidemia [5]. Their reduction has been shown to lower the incidence of coronary heart disease (CHD) among individuals with dyslipidemia and the frequency of CHD-related death in patients who already have CHD [6]. The current drug therapy for treatment of hypercholesterolemia according to [7] are Bile acid sequestrants, Nicotinic acid, estrogen replacement therapy, fibrates and statins [8-11]. This drug therapy are reserved for cases that cannot be managed with therapeutic lifestyle changes alone and/or those characterized by substantial cardiovascular risk [6]. The guidelines for management of hypercholesterolemia formulated by the National Cholesterol Education Program (NCEP) and ATP III emphasize the use of dietary modifications, weight loss and physical activity. On the other hand, high levels of dietary fat have been reported to induce oxidative stress, overproduce reactive oxygen species (ROS) and decrease antioxidative enzyme activity [4, 12]. Increased oxidative stress, appears to play an important role in the chronic inflammatory responses to hypercholesterolemia and atherosclerosis [2, 4, 12, 13]. Therefore, apart from hypocholesterolemic drug intervention in reducing blood cholesterol level, the use of antioxidant therapy which has been extensively evaluated in different studies [12-14].

Alpha-Lipoic acid, a natural compound widely distributed in plants and animals, functions as a cofactor within mitochondrial enzymes to catalyze the oxidative decarboxylation of α-keto acids (such as pyruvatedehydrogenase and α-ketoglutarate dehydrogenase) and glycine cleavage [15-17]. Aside from its role in the mitochondrial metabolic pathway, α-lipoic acid when supplemented in diets induces various physiological activities in experimental animals and in humans [16, 17].

Alpha-Lipoic acid and α-dihydrolipoic acid are powerful antioxidants; therefore, dietary lipoic acid is effective in attenuating oxidative stress induced by drugs [18], a high-fructose diet [19], aging [20] and physical exercise [21]. Also, α-lipoic acid protected against oxidative stress induced by active oxygen in cultured cells [22, 23]. Alpha lipoic acid is capable to alterate hepatic fatty acid [24] and oxidation [25] and thus it modify the availability of fatty acids for the synthesis of triacylglycerol and in turn alter very-low-density lipoprotein production by the liver; therefore, a change in the rate of these metabolic processes is crucial to decrease serum lipid concentrations [26].

Panax ginseng C.A. Meyer, also known as Korean ginseng, is one of the most renowned herbal plants worldwide and has been used for thousands of years to maintain homeostasis of the body and enhance vital energy, particularly in Asian countries [27].To date, numerous studies have demonstrated the pharmaceutical effects of P. ginseng on physical, chemical and biological stress [28], systemic immune function [29], glucose metabolism [30], sexual function [31] and mental capacity [32]. Several active compounds, including polyacetylenes, esquiterpenes, peptidoglycans, polysaccharides and approximately 40 ginsenosides, have been identified in P. ginseng [33]. Antioxidative effects of P. ginseng have been detected in animal studies [34, 35].One of the mechanisms underlying the health-related benefits may be associated with its antioxidant properties. Many reports from clinical and experimental studies suggested that ginseng may have beneficial effects as an anti-hyperlipidemic agent on reducing serum total cholesterol level and enhancing antioxidant status [36, 37]. However, Ismail *et al*.[66] reported that ginseng extract, G-115 in rabbits has no significant hypolipidemic or antioxidant potential. Recently, evidence-based complementary and alternative medicines have become important factors in the clinical use of herbal remedies [38] thus the present study was conducted to evaluate the antihypercholesterolemic effect of α- lipoic acid and panax ginseng.

MATERIALS AND METHODS

The present study was conducted on forty adult newly investigated hypercholesterolemic patients, ranging in age from 40 to 60 years, who were recruited from the outpatient department of Medicine at Misr University for Science and Technology (MUST). Patients did not take any antioxidants or antihypercholesterolemic agents or any drugs which may interfere with the results. Exclusion criteria were use of supplements containing LA and/or ginseng, pregnancy before or during the study, presence of renal failure and liver cirrhosis, change or introduction of new medication to the treatment of hypercholesterolemia during the study. Each eligible subject received one of the following treatments: capsules containing 600 mg LA (Thiotacid tablets, 600 mg, EVA Pharma for Pharmaceuticals and Medical Appliances,

Egypt) (LA group), capsules containing 100 mg ginseng (ginsana capsule, 100 mg, EIPICO Pharmaceutical Company, Egypt) (ginseng group) and placebo. The supplements were taken daily for a period of 8 weeks. The participants were advised to perform exercise one hour daily and to consume low fat diet. Informed consent was obtained from each subject.

Study Protocol: The subjects were divided into alpha lipoic acid group (20 hypercholesterolemic patients), ginseng group (20 hypercholesterolemic patients) and control group (20 healthy subjects). Each subjects of α- lipoic acid group ingested two capsules (600 mg each) two times a day. The ginseng group was ingested two capsules (100 mg each) two times a day and the treatment protocol continued for 8 weeks. Blood samples were collected after four weeks and after eight weeks of the treatment period. All subjects were fasted for 12 h for the determination of serum lipids markers.

Laboratory Measurements: 10 ml of venous blood were collected in heparinized tube from each patient (after 10-12 hr overnight fast). All patients were subjected to routine laboratory investigations including complete blood count, hemoglobin concentration, serum creatinine, blood sugar, blood urea, serum potassium and sodium as well as liver enzymes (ALT and AST). Also, all patients were informed to decrease fatty diet and perform one hour exercise daily.

These laboratory investigations have been carried out to select patients with normal blood profile and liver and kidney functions. Any patient displaying abnormal parameter (s) was excluded. After collection, samples were centrifuged at 2500 rpm for 10 mints. Then they were placed immediately in ice and protected from light. Both plasma and erythrocyte fraction will kept frozen until analysis. Serum TC, HDL-c, TG and LDL were measured by validated routine enzymatic and colorimetric methods using cobas c 111 system. LDL-c was estimated using the Friedewald equation.

Statistical Analysis: Differences among the treatment effects were statistically significant ($p < 0.05$). Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12). Mean, standard deviation and range were used for description of the sample. NOVA test was used to compare more than two groups as regard quantitative variables.

RESULTS

Lipid Profile Parameters: The current data revealed that administration of α-lipoic acid (600 mg twice daily) for one month significantly lowered low density lipoprotein levels, while after two months both low density lipoprotein and total cholesterol were significantly reduced as compared to newly diagnosed hypercholesterolemic patients (Table 1, Figs. 1,2).

Administration of panax ginseng (100 mg twice daily) for one or two months showed a significant reduction in low-density lipoprotein, total cholesterol and LDL/HDL and CHOL/HDL ratio as compared to hypercholesterolemic patients (Table 2, Figs. 3,4).

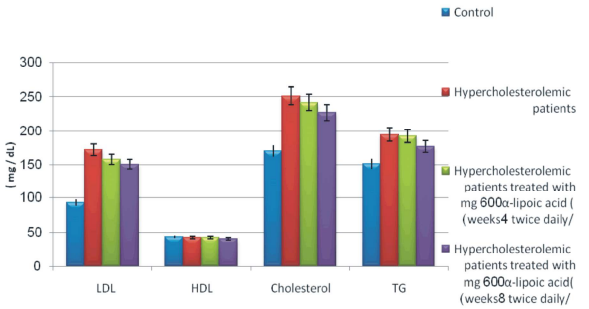

Fig. 1: Showed lipid profile levels before and after α-lipoic acid treatment.

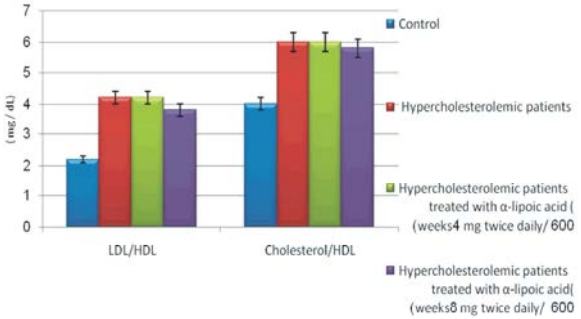

Fig. 2: LDL/HDL and CHOL/HDL ratios before and after α-lipoic acid treatment.

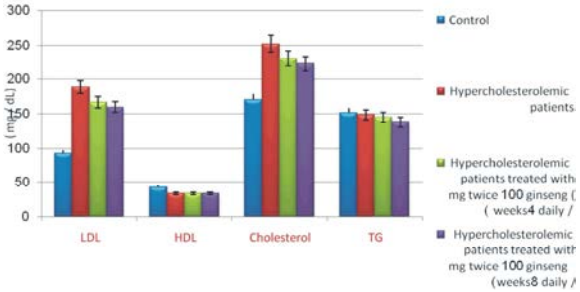

Fig. 3: lipid profile levels before and after ginseng treatment.

Table 1: Effect of 4 weeks or 8 weeks treatment of newly investigated hypercholesterolemic patients with alpha-lipoic acid on lipid profile parameters as compared with control volunteers

Parameters measured	Group 1 Control	Group 2 Hypercholesterole -mic patients	Group 3 Hypercholesterole-mic patients treated with α-lipoic acid (600mg twice daily/ 4 weeks)	Group 4 Hypercholesterolemic patients treated with α-lipoic acid (600mg twice daily/ 8 weeks)
LDL (mg / dL)	92.8±23	171.9±23[a]	158±32[a,b]	150.7±33[a,b]
HDL (mg / dL)	43.2±6	42.3±10[a]	42±10	40.6±8.9
Cholesterol (mg / dL)	170±17	251±20[a]	241.3±34[a]	227±33[a,b,c]
TG (mg / dL)	151±40	194.6±60	192±80[a]	177±73[a]
LDL/HDL (mg / dL)	2.2±0.8	4.2±1.1[a]	4.2±1.6[a]	3.8±1.2[a]
Cholesterol/HDL (mg/dL)	4±0.9	6±1.4[a]	6±1.9[a]	5.8±1.5[a]

Each value represents the mean ± SD (n= 20)

[a]= significantly different from control group value at p= 0.05.

[b]= significantly different from hypercholesterolemic group value at p= 0.05.

[c]= significantly different from α-lipoic acid treated group value (4 weeks) at p= 0.05.

Table 2: Effect of 4 weeks or 8 weeks treatment of newly investigated hypercholesterolemic patients with ginseng on lipid profile parameters as compared with control volunteers

Parameters measured	Group 1 Control	Group 2 Hypercholesterolemic patients	Group 3 Hypercholesterolemic patients treated with ginseng (100 mg twice daily / 4 weeks)	Group 4 Hypercholesterolemic patients treated with ginseng (100 mg twice daily / 8 weeks)
LDL (mg / dL)	92.8±23	188.6±22[a]	167±17[a,b]	159.8±12[a,b,c]
HDL (mg / dL)	43.2±6	33.9±6[a]	33.9±4.9[a]	34±4.8[a]
Cholesterol (mg / dL)	170±17	252±18[a]	230.5±15[a,b]	222.5±11[a,b,c]
TG (mg / dL)	151±40	148.7±50[a]	144.9±22[a]	138±33.8[a]
LDL/HDL (mg / dL)	2.2±0.8	5.8±1.5[a]	5±1.08[a,b]	4.8±0.97[a,b,c]
Cholesterol/HDL (mg / dL)	4±0.9	7.7±1.7[a]	6.8±1.2[a,b]	6.7±1[a,b]

Each value represents the mean ± SD (n= 20)

[a]= significantly different from control group value at p= 0.05.

[b]= significantly different from hypercholsterolemicgroup value at p= 0.05.

[c]= significantly different from ginseng treated group value (4 weeks) at p= 0.05.

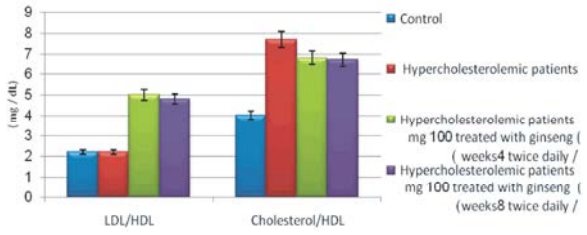

Fig. 4: LDL/HDL and CHOL/HDL ratios before and after ginseng treatment..

DISCUSSION

Hypercholesterolemia is a major cause of cardiovascular disease (CVD), such as atherosclerosis and coronary heart disease [39]. Although several factors, such as cigarette smoking, high-fat diet, high blood pressure, physical inactivity, age and heredity have significant roles in causing CVD, high blood cholesterol is mainly responsible for the onset of CVD [40,41]. Lowering serum cholesterol levels by drug or dietary interventions could reduce the risk of CVD [42, 43].

Many patients prefer non drug therapies for many reasons including adverse effects of antihyperlipidemic drugs, contraindications or allergic reactions to drugs or perceptions of adverse effects of drugs; therefore it is worthwhile to develop new safe and effective cholesterol-lowering agents from natural products. Studies have shown that vitamins and nutritional supplements including fiber, garlic and yeast may reduce one's total and LDL cholesterol levels. α-lipoic acid and ginseng are examples of antioxidant which have been investigated as therapeutic alternatives to diminish cerebral damage, with varying results [42,44-46].

Since hypercholesterolemia may be accompanied to diseases as hypertension and diabetes, use of α-lipoic acid may be beneficial in controlling these disorders [47]. The aim of this work was to evaluate the effect of α-lipoic acid and ginseng on newly investigated hypercholesterolemic patients.

Results of the current study showed that four weeks treatment of hypercholesterolemic patients with α-Lipoic acid (600 mg twice daily before breakfast and dinner, for four weeks) significantly lowered LDL only with no effect

on the other parameters. However, after eight weeks, both LDL and TC were significantly low as compared to hypercholesterolemic patients. The current study is in agreement with [26] who showed that α-lipoic acid lowered concentration of TC levels in animal models. [48] Showed that levels of blood levels of TC and LDL were found to be reduced after administration of α-lipoic acid for ten weeks. Previous studies reported that α-lipoic acid supplement decreased TC, LDL and TG levels while HDL levels was increased in animal models [49, 50]. The improvement in TG and HDL in addition to TC and LDL may be due to difference in animal and human models. Also, the current study is in agreement with [51] who reported that α-lipoic acid improved cholesterol levels and glucose tolerance in Participants with impaired glucose tolerance in human models.

The mechanism on how α-lipoic acid able to reduce TC and LDL levels is unknown. This mechanism may be probably due to lipoprotein lipase (LPL) activity or through cholesterol metabolism by the liver [52]. α-lipoic acid probably capable to initiate LDL receptor synthesis in the liver which in turn increase the uptake of cholesterol back to the hepatic system and increase synthesis of apoprotein A component (moiety of HDL particles) for reversed cholesterol transport [53].

On the other hand [35] showed a reduction of VLDL and TG in animal models. In the contrary, the present study revealed no change of triglycerides or VLDL. Therefore this difference also may be due to difference in human and animal models.

In contrast to our results [54, 53] showed that α-lipoic acid did not affect the lipid profile parameters. The difference between the previous studies and the current study may be due to difference in the dose and duration of α-lipoic acid as the dose in the current study was 600 mg twice daily for eight weeks while the dose in the previous studies was 600 mg once a day for eighteen weeks.

Panax ginseng is one of the most well-known herbal health tonics worldwide. The drug is traditionally believed to strengthen general health and boost vital energy [27]. Several animal and clinical studies have provide scientific evidence for various health benefits of ginseng, including immunomodulation [29], increased cognitive function [55], reduction of fatigue [56], biological stress [28], improved glucose metabolism [31] and sexual function [32] and cancer prevention [57]. American Ginseng (Panaxquinquefolius L.) and Asian ginseng (Panax ginseng C.A. Meyer) are the two major species of ginseng having been used in various traditional medicinal therapies for many years in China. They differ in the quantities of the specific ginsenosides on anticarcinogenic effects [57].

The current study revealed that administration of panax ginseng (100 mg twice daily, for four or eight weeks) showed a significant reduction in LDL, TC, LDL/HDL and CHOL/HDL ratios as compared to hypercholesterolemic patients. These results are in agreement with [58] who showed a reduction in TC level after ginseng administration in rabbits. It was previously reported that ginseng saponins decrease blood cholesterol levels in prolonged cholesterol fed rabbits by increasing cholesterol excretion through bile acid formation [59, 60] and ginsenoside-Rb2 as one of active components of ginseng saponins may accelerate serum cholesterol turnover by increased cholesterol degradation and excretion in the feces, which was observed in the case of Panax ginseng administration to normal rats [60]. Also [61] showed that administration of korean red ginseng extract (KRGE) reduces the levels of TC, LDL and serum TG. The difference between the previous study and the current study may be due to difference between animal and human models.

Also human studies supported our results. Kim *et al*. [62] showed that Serum TC, TG, LDL levels were reduced significantly by administration of PGE (2 g per day, for two weeks) moreover, HDL levels was increased. In the present work the administration of panax ginseng has no effect on TG and HDL. The difference between the present study and the previous study may be due to difference in the dose used for treatment as the dose of the current study was 100 mg twice daily while the previous study used a larger dose which is 2 g per day. Also, the present results were supported by the Report that long-term administration of red ginseng products in obese women reduced cholesterol levels [63].

The mechanisms of panax ginseng in treating hypercholesterolemia is that Panax ginseng extracts elevate antioxidant potentials by decreasing malondialdehyde levels and by increasing erythrocyte superoxide dismutase which acts as a scavenger to reduce hypercholesterolemia [62]. Ginseng saponins as ginsenosides increase LDL receptors by promoting the synthesis of LDL receptors in rats [40]. Based on the studies reported, it was thought that those action mechanisms of Panax ginseng components on lipid metabolism might be involved in the present study. Also, Kim *et al*. [64] confirm the antioxidant activity of P. ginseng in healthy subjects, as it enhanced the antioxidant system, which specifically decreased

generation of reactive oxygen species (ROS) and effectively decreased serum malondialdehyde (MDA) levels. This reduction of antioxidant activity is the cause of the hypolipidemic effect of panax ginseng [62] which is consistent with the present result.

However, controversy still exists in animal studies. Ismail *et al*. [65] reported that ginseng extract, G-115 in rabbits did not show any significant hypolipidemic or antioxidant potential. Also, in contrary to the present study, Hong *et al*. [66] showed that eight weeks of oral ginseng administration decreased serum level of TG and increased the levels of HDL significantly with no effect on LDL or TC. The difference between the previous study and the current study may be due to difference in animal and human models.

In The current study, the administration of ginseng extract, G-115 significantly lowered LDL, LDL/HDL and cholesterol with no effect on TG. However, KWAK *et al.* [67] showed that oral administration of red ginseng acidic polysaccharide (100 to 1000 mg/kg) dose-dependently reduced the serum levels of TG in rats and such reduction effects were not observed in TC and phospholipid levels. Moreover, Liu *et al*. [68] demonstrated that pancreatic lipase inhibitor of protopanaxdiol (type ofginsenosides from isolated from the leaves of American ginseng) was significantly effective in preventing and ameliorating obesity, fatty liver and hypertriglyceridemia in mice fed with a high-fat diet. The previous studies and the current results suggest that the whole parts of ginseng plant may play an additional role in reducing hyperlipidemic conditions.

Although this study showed an improvement in LDL and TC in newly investigated hypercholesterolemic patients after α-lipoic acid administration for two months, the improvement effects of panax ginseng was shown to be more effective in reducing LDL, TC, LDL/HDL and CHOL/HDL ratio. Panax ginseng may be a useful substance for prevention and treatment of hyperlipidemia in human. Because of the content of ginsenosides in different parts of panax ginseng, further studies of monomer ginsenosides on antihyperlipidemic effect is necessary. In conclusion the current study panax ginseng supplement may be useful in improving hyperlipidaemia more than α-lipoic acid in newly investigated hypercholesterolemic patients.

These results, together with the existing evidence, justify long-term investigations to evaluate the use of these drugs in the treatment of hypercholesterolemic patients. The dose of panax ginseng may be increased to achieve the desired results also, the combination of the two antioxidants must be encouraged.

Conflict of Interest: The authors declare that there are no conflicts of interest.

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