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The protective effects of ginger on the development of coronary atherosclerosis: An experimental animal study

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ABSTRACT

The use of ginger extracts has been recently suggested to be effective for prevention of establishing and development of coronary atherosclerosis due to its antioxidant and anti-inflammatory components. In the present study, the effect of standardized ginger extract on the development of experimentally induced atherosclerosis in animal models was investigated. The study protocol was consist of three groups of male rabbits (n = 5 each group) that were randomly divided to three groups to fed a common stock diet (containing bran and fresh vegetables) plus high cholesterol pack, or stock diet plus ginger (0.1 g/kg body weight/day) (group II) together with cholesterol, or only stock diet as the atheroma control for 75 days. Atheroma was graded macroscopically by mean graticule count percent. The degree of experimental cholesterol atherosclerosis was graded on an arbitrary scale of 0 to 4, and serum level of total cholesterol was also measured. The atherosclerotic lesion area was macroscopically smaller in rabbits that consumed ginger in comparison with the lesion area in those animals no received ginger extract (43.26 ± 8.7 mm^2 versus 82.3 ± 7.9 mm^2, $p<0.001$). Microscopically, the mean grading in coronary artery of rabbits received high cholesterol diet without ginger was 3.1±0.56, while in the group received high cholesterol diet plus ginger was 1.6±0.85 with a significant difference. Regarding effects of ginger on total cholesterol level and considering non-significant cholesterol level at baseline, the level of cholesterol after 75 days reached 66.72±0.12 mg/dL in the control group, 776±40.55 mg/dL in group fed high cholesterol without ginger, and 446±23.97 mg/dL in the group fed ginger with a significant level in high cholesterol plus ginger group than in high cholesterol alone group ($p<0.001$). Ginger can effectively protect the development of atherosclerosis manifested by lowering serum cholesterol level, as well as reducing infarct size and grade.

Keywords: Atherosclerosis, Coronary artery, Ginger, Cholesterol, Rabbits.

INTRODUCTION

Globally, according to the recent report of the American Heart Association, coronary artery disease (CAD) has been shown as the most frequent form of cardiovascular diseases [1]. This ischemic event is responsible for the highest mortality rate in most developed and developing countries such as Iran that accounts for nearly 50 percent of all deaths per year [2]. CAD mainly develops as clustering various traditional risk factors including elevated blood sugar, current smoking, hypertension, and increased levels of total cholesterol and low density lipoprotein as well as reduced level of high density lipoprotein. The development of these general risk factors results in inducing and

activating some pathological processes such as lipids oxidation, platelet aggregation, and inflammatory pathways, leading coronary atherosclerosis [3]. For many years, the fundamental role of traditional medicine in treating and preventing cardiovascular disorders and related risk factors has been widely evaluated and clearly demonstrated as a safe and effective therapeutic option [4-7]. In traditional medicine, medicinal plants are a main resource for discovering new drugs [8-11]. They have been used in traditional medicine for prevention of various human disorders [12-19]. So in a lot of studies, the effects of them have been investigated [20-26]. They have been shown the antioxidant activity, anti-inflammatory, anti-hyperlipidemic effects, etc. They can be effective for prevention and tretment of CAD. In this regard, the consumption of some herbal extracts with phenolic flavonoids has been shown to be associated with considerably reduced morbidity and even mortality in CAD patients [27]. In this context, it can be pointed to beneficial effects of ginger by virtue of its lipid lowering, antianginal, antioxidant, anti-inflammatory, and thus cardioprotective effects [27, 28]. Ginger (*Zingiber officinale* Rosc.) belongs to the family Zingiberaceae that originated throughout the world especially in Asia [29]. For very long years, the extracts of this herb is used in traditional herbal medicine. Because of the inflammatory and oxidative natures of coronary atherosclerosis, it has been recently suggested that the use of ginger extracts can effectively prevent establishing and development of coronary atherosclerosis due to its antioxidant and anti-inflammatory components.

In the present study, the effect of standardized ginger extract on the development of experimentally induced atherosclerosis in animal models was investigated.

MATERIALS AND METHODS

The study protocol was consist of three groups of male rabbits weighing 1.0–1.5 kg (n=5 each group) and each group were randomly divided to three groups to fed a common stock diet (containing bran and fresh vegetables) plus high cholesterol pack (0.3 g/kg body weight daily suspended in 5 ml of milk) (group I), or stock diet plus ginger (0.1 g/kg body weight/day) (group II) together with cholesterol mixed with 5 ml milk, or only stock diet as the atheroma control (group III). Ginger ethanolic extract was prepared from concentrated pure ginger powder. The ginger extract was standardized to contain 40 mg/g of total pungent compounds (gingerols, shogaols and zingerone), 90 mg/g of total polyphenols and 14 mL/g of essential oils [30]. The three groups of experiments fed for 75 days. The animals also drank their water equally. After 75 days of follow-up time, the study groups were anesthetized intraperitoanally with ketamine (4 mg/100 g) and xylazine and then killed and autopsy samples of coronary arteries were examined for atherosclerosis assessment. The samples were fixed overnight in 2.5% glutaraldehyde with cacodylate buffer (0.2 mol/L), serially dehydrated in alcohol, and embedded in paraffin. Light microscopy was performed on 5-µm-thick tissue sections mounted on glass slides and stained with hematoxylin and eosin. The sections were examined by a pathologist who was unaware of experimental protocol. Atheroma was graded macroscopically by mean graticule count percent that has been previously described. Briefly, the size of the atherosclerotic lesions was measured microscopically using a special lens called agraticule to see if the lesion decreased in size [31]. The degree of experimental cholesterol atherosclerosis observed in each animal was graded on an arbitrary scale of 0 to 4 based on Duff and colleagues. Total serum cholesterol was also obtained by enzymatic assays of blood samples collected from the rabbits at baseline and also immediately before they were killed. The maximum values accepted as normal total serum cholesterol 80 mg. percent [32]. Platelet count was also determined from blood samples by a Coulter counter. Measured data were reported as mean±SD or number (percentage). For statistical analysis, overall comparison among the three groups was conducted with Fisher's exact test and the Kruskal-Wallis test for discrete and continuous data, respectively. Comparisons between any two groups of rabbits were made by an exact Wilcoxon mid rank test. Diet-induced changes in serum cholesterol were compared by paired Student's t test. A p-value of <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

A section of coronary arteries derived from all animal samples studied in the three groups showed the presence of atherosclerotic lesions in the two groups which fed with high cholesterol pack after 75 days. No atherosclerotic lesion was observed in control group fed with stock diet alone. The atherosclerotic lesion area was macroscopically smaller in rabbits that consumed ginger in comparison with the lesion area in those animals no received ginger extract (43.26±8.7 mm^2 versus 82.3 ± 7.9 mm^2, $p<0.001$). Microscopically, the mean grading in coronary artery of rabbits received high cholesterol diet without ginger was 3.1±0.56, while in the group received high cholesterol diet plus ginger was 1.6±0.85 with a significant differences, appearing a meaningful reduction in atheroma size in

coronary artery. Regarding effects of ginger on total cholesterol level, the baseline level of serum total cholesterol in the group with stock diet alone was 62.66±0.85 mg/dL, in cholesterol fed group was 64.12±0.66 mg/dL, and in cholesterol plus ginger fed group was 61.23±0.42 mg/dL with no significant difference, while these rates following consuming regimen after 75 days reached 66.72±0.12 mg/dL, 776±40.55 mg/dL, and 446±23.97 mg/dL with a significant level in high cholesterol plus ginger group than in high cholesterol alone group ($p<0.001$).

According to our study findings, the infarct size induced by high-cholesterol regimen as well as its microscopically assessed grade was significantly reduced following consumption of ginger; however these indices were unchanged in another experimental group and in control group, indicating high effectiveness of ginger for reducing the size of infarct area following feeding ginger extract for 75 days in animals. Furthermore, the use of ginger in combination with high-cholesterol diet significantly decreased serum total cholesterol in rabbits predisposed to myocardial infarction. On the other hand, the consumption of ginger extract led to considerably reduce serum cholesterol level inducing infarction in animal models and thus the examined models experienced lower risk of infarction following use of ginger. Within recent decades, research laboratories have provided strong scientific support for the long-held belief that ginger contains constituents with properties lowering cardiac infarction and its-related risk profile. It has been clearly demonstrated that the main fundaments of cardiac infarction include activation of inflammatory processes, aggregation of platelets, and production of oxidants that all induced by appearing a rupture on coronary plaque. In this regard, the beneficial effects of ginger on these different processes have been recently studied. Some recent discoveries have provided the evidences that ginger modulates biochemical pathways activated in chronic inflammation [33]. Antioxidants have been shown to reduce oxidative stress and prevent the complications induced by it [34-36]. Also, the anti-oxidative properties of this herb has been revealed. The main antioxidant principles in ginger include the gingerols and shogaols and some related phenolic ketone derivatives. Ginger extract possesses antioxidative characteristics gingerol from ginger inhibited, at high concentrations, ascorbate/ferrous complex induced lipid peroxidation in liver microsomes [37]. With respect to inhibitory effects of ginger on platelet aggregation, gingerol isolated from zingiber was shown to inhibit platelet function due to inhibition of thromboxane formation [38].

Along with the direct effects of ginger on atherosclerosis stimulating factors such as inflammatory, oxidative, and coagulative processes, the role of this herb as a hypolipidemic agent has been also shown in line with our experiment [39]. In a similar study by Verma and colleagues, there was distinct decrease in lipid peroxidation and its serum level in atherosclerotic rabbits [40]. Also, in Fuhrman et al. study; the consumption of 250 µgr of ginger extract per day resulted in significant reductions in plasma triglycerides and cholesterol, in VLDL, and in LDL and also was associated with a 76% reduction in cellular cholesterol biosynthesis rate [30].

According to recent researches, the main biochemical effect of ginger is reducing lipids peroxidation that may be attributed to its antioxidant activity as it contains many phenolic compounds which have inhibitory effect on lipid peroxidation [41]. This explanation was agreed with Ahmed et al. who reported that ginger significantly lowered lipid peroxidation by ameliorating the activities of the antioxidant enzymes; superoxide dismutase (SOD), catalase and glutathione peroxidase in rats [42]. Moreover, Sujatha and Srinivas revealed that the aqueous extract of ginger inhibited lipid peroxidation and formation of diene, triene and tetraene conjugates in human erythrocyte membrane [43]. This concept has also been revealed with other plants having antioxidant activities [44-57]. The hypolipidemic effect of ginger may be also attributed to stimulation of the conversion of cholesterol to bile acids, an important pathway of elimination of cholesterol from the body by ginger, leading reduction of serum level of cholesterol [4]. In total, further studies should be conducted to clear any pathways involving lipid lowering by administration of ginger.

CONCLUSION

The use of ginger extract can reduce development of infarct size and it's microscopically grade and also can reduce serum level of cholesterol in animal models. For confirming these effects on human, more researches should be performed.

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