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COMPARATIVE HYPOLIPIDEMIC EFFECTS OF GINGER (*ZINGIBER OFFICINALE*) AND LOVASTATIN IN CHOLESTEROL FED RABBITS

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ABSTRACT

Hyperlipidaemia is one of the major contributors to atherosclerosis and coronary heart disease in our society. Non-pharmacological therapy especially dietary therapy and exercise are the first line of treatment in hyperlipidaemia, however pharmacotherapy is used in patients who are at high risk of coronary heart disease or patients who do not respond to non-pharmacological therapy. Present study is designed to investigate the effectiveness of fresh grated ginger (*Zingiber officinale*) administration over statin therapy. Age matched female rabbits were divided into three experimental groups. Base line values of all parameters were observed and animals were then administered atherogenic diet for four weeks. Lovastatin were fed @ 200mg/kg of body weight/ day ginger and 20mg/kg of body weight /day to these hypercholesterolemic rabbits for another four weeks. At the end of experimental period blood specimens were obtained and assayed for alterations in plasma lipid profile and glutamate pyruvate transaminase levels. Results of the present study were showed that both ginger and lovastatin reduce plasma cholesterol, LDL-C and triglyceride levels and increase plasma HDL-C levels, but significant results were obtained with lovastatin therapy. GPT levels were significantly reduced only with ginger administration. These findings suggests that dietary supplementation of ginger alone cannot be used effectively for secondary prevention trials, but for primary prevention trials due to adverse effects of Lovastatin on liver functions it can be used effectively.

Key-words: Ginger, Hypercholesterolemia, Atherosclerosis, Hypolipidemic effects, Lovastatin, Rabbits.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in the developed world (National Center for Health Statistics, 1993), and atherosclerosis, the principal cause of myocardial and cerebral infarctions, accounts for the major cause of these deaths in the United States and Western Europe (Ross, 1986). In U.S. alone there are approximately 1 million deaths attributable to CVD each year (National Center for Health Statistics, 1995). The most common and important cause of premature coronary artery disease is known to be the lipid disorders. The role played by dyslipidemia in the genesis of coronary atherosclerosis is well established. And more specifically, high levels of total cholesterol and low density lipoprotein (LDL) cholesterol, reduction in high density lipoprotein (HDL) cholesterol and increase in triglyceride (TG) levels predispose to coronary disease (Castelli, 1998). Substantial evidence from basic and clinical research suggests that atherosclerosis can be prevented and that its progression can be retarded. Generally two options are available for the treatment of coronary artery disease (CAD) i.e Primary and secondary prevention trials. Reduction in the concentration of serum lipids, especially cholesterol, is a major goal in several primary and secondary prevention initiatives. That cholesterol-lowering drugs decrease mortality due to cardiovascular disease is unequivocal. The use of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (statins) in clinical trials over the last 11 years supports this conclusion in a variety of populations, including patients with or without established cardiovascular disease and patients with severe or only moderate hypercholesterolemia (Anonymous, 1994; Anonymous, 1998; Shepherd *et al*., 1995; Hebert *et al*., 1997). How ever use of pharmacological therapy in persons with out known CAD is still controversial. Unfortunately, sudden cardiac death at the time of the first myocardial infarction is common, so awaiting to treat until symptoms of CAD have developed will never be an acceptable strategy, because the first symptom of CAD is too often a sudden death. Non pharmacological approach includes dietary therapies. Diet plays an important role in the primary and secondary prevention of coronary artery disease (Stone, 1998). Ginger is an undried rhizome of the plant, *Zingiber Officinale* Roxoe. It is one of the world's best known spices, and it has also been universally used throughout history for its health benefits (Fuhrman et al., 2000). Many previous studies suggest the hypolipidemic role of ginger in animal models (Gujaral *et al*., 1978; Giri *et al*., 1984). Present study is undertaken with a task to evaluate the role of fresh ginger in lowering blood cholesterol levels in hypercholesterolemic animals and hence its importance as non pharmacologic mean for prevention of coronary artery disease in general.

MATERIALS AND METHODS

Animals: A total of 30 female white rabbits were used. The animals were two months old at the start of experiment, and had a mean body weight of 1.5-2 kg.

Experimental Protocol:

Initially all the rabbits were kept for acclimatization for about one week. The body weights and other physical conditions were closely monitored through out the study. After an overnight fast, blood was drawn from the marginal ear vein and plasma base line values for all parameters were checked. Rabbits were then randomly divided into three groups. Group I (n = 10) animals were fed normal rabbit chow and served as control. Group II (n = 10) and group III (n = 10) animals received an atherogenic diet (1g butter fat / 100g of daily diet) for four weeks (Moghadasian *et al*., 1999). Food and water were provided ad libitum during the study and food intake was recorded periodically to avoid differences between groups in the amount of feed consumed. After four weeks: Group II animals were maintained on atherogenic diet and in addition received 20mg/kg of body weight lovastatin orally for four weeks (McKenney *et al*., 1995; Kastrup, 1998). Group III animals together with atherogenic diet received fresh grated ginger 200 mg/kg of body weight orally for four weeks (Bhandari *et al*., 1998). Blood samples were collected from all the animals after every dietary modification and body weight, plasma lipid profile, and levels of glutamate pyruvate transaminase (GPT) were measured.

Biochemical Analysis:

Plasma cholesterol and triglyceride levels were measured using enzymatic kit (Clonital Italy), Serum HDL-C levels were measured by dextran sulphate Mg (II) method, using enzymatic kit (QCA, France). Serum LDL-C concentration was determined by polyvinyl sulphate method using enzymatic kit (QCA France). Serum GPT levels were determined calorimetrically using enzymatic kits (Randox, UK).

Statistical Analysis:

The data expressed as mean ± S.E.M. and were analyzed by analysis of variance (ANOVA) and by t-test. A value of $P < 0.05$ was chosen as the criteria of statistical significance.

RESULTS

Pathogenesis of Hypercholesterolemia: The Plasma total cholesterol, triglyceride, HDL-C , LDL-C, GPT levels and body weights in rabbits fed on normal chow diet (group I) were remain stable throughout the experimental period (Table 1). With hypercholesterolemic diet significant rise in total body weight (16%), plasma cholesterol (22%), triglyceride (4 fold rise) and lipoproteins levels (2 fold rise in both HDL-C, LDL -C) were observed. Plasma GPT levels were non significantly increase by 7%.

Table 1. Comparative effect of ginger and lovastatin on plasma lipid profile, GPT and Glutathione levels in experimental rabbits.

	Experimental Groups			
Parameters	**Control**	**Hypercholesterolemic**	**Lovastatin Treated**	**Ginger Treated**
Body weight (gm)	1313 ± 65.5	1526.3 ± 52	1340.6 ± 54.3	1432.5 ± 38.7
Cholesterol(mg/dl)	22.68 ± 1.26	124.56 ± 3.61	103.65 ± 1.16	109.52 ± 1.10
HDL-C (mg/dl)	22.28 ± 2.57	44.81 ± 3.42	54.78 ± 0.82	48.18 ± 1.41
LDL-C (mg/dl)	15.58 ± 2.9	35.74 ± 2.07	22.35 ± 0.57	25.73 ± 1.02
Triglyceride (mg/dl)	35.01±1.14	152.23 ± 0.91	129.99 ± 6.30	130.55 ± 3.43
GPT (UI/L)	13.7 ± 0.59	14.6 ± 0.47	16.8 ± 0.55	10.3 ± 0.39

HDL-C= High density lipoprotein cholesterol; LDL-C= Low density lipoprotein cholesterol; GPT= Glutamate pyruvate transaminase. All values are in mean ± SEM. n = 10

Effect of ginger and lovastatin on hypercholesterolemic rabbits: Ginger and lovastatin produced significant antihyperlipidemic action. They both significantly ($P < 0.05$) reduce the levels of plasma cholesterol, triglyceride and LDL-C as compared to hypercholesterolemic groups. HDL-C levels were increased with both ginger and lovastatin administration (Table 1) but significant increase ($P<0.05$) was observed only with lovastatin. Total body weights of animals were significantly reduced with the administration of both ginger and lovastatin but more significant reduction were obtained with lovastatin. Plasma GPT levels were significantly increased (15%) with administration of lovastatin as compared to hypercholesterolemic group (Table 1). However, ginger lowers plasma GPT concentration in hypercholesterolemics below the normal levels.

DISCUSSION

Atherosclerosis is a multi factorial disease associated with different risk factors. Hypercholesterolemia is a major risk factor for atherosclerosis (Dominiczak, 1998). It indicates the onset of abnormalities in lipid metabolism. Recently non-pharmacological therapies received world wide attention for the treatment of hyperlipidemia (Bhandari *et al*., 1998). In the present study we have investigated the effectiveness of antihyperlipidemic action of ginger in cholesterol fed rabbits compared to the pharmacologic therapy of Lovastatin. Results of the present study were showing that 200mg / kg of body weight/ day ginger administration in hypercholesterolemic rabbits produced a significant decrease in plasma cholesterol, triglyceride and LDL-C levels and a prominent rise in HDL-C levels in hypercholesterolemic rabbits. According to Srinivasan and Sambaiah (1991) this protective hypolipidemic effect of ginger may due to enhanced activity of hepatic cholesterol-7 alpha hydroxylase enzyme, which is a rate limiting enzyme in bile acid biosynthesis, increase activity of this enzyme stimulate the conversion of cholesterol to bile acid. Compared to ginger, Lovastatin administration show more significant reduction in plasma cholesterol, triglyceride, and LDL-C levels and a significant rise in HDL -C levels. Research studies in humans prove that Lovastatin in 20-80mg doses/day show 15-35% decrease in total cholesterol, 7-25% decrease in triglyceride, 20-35% decrease in LDL-C and 2-15% increase in HDL-C concentrations (McKenney *et al*., 1995; Kastrup, 1998). Results of the present study nearly following the same pattern. Lovastatin is a 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitor which inhibit the reduction of HMG CoA into mevalonate, an important step in synthesis of cholesterol (Verschuren *et al*., 1995). Statin treatment also result in the up regulation of LDL receptors by hepatocytes, increase the plasma concentration of apo A-1 (Schaefer *et al*., 1999). These are the beneficial effect of lovastatin in prevention of coronary heart disease (CHD) in patients with hypercholesterolemia. Hepatotoxicity has been described with all statins and usually manifests as asymptomatic elevations of serum transaminases (aminotransferases). Persistent elevation greater than three times the upper limit of normal are considered significant, and treatment should be discontinued if this occurs, hepatotoxicity with statin appears to be dose related (Zhao *et al*., 2003). The results of present study were showing elevated GPT levels in hypercholesterolemic rabbits treated with Lovastatin. This type of elevation was not observed in rabbits receiving fresh grated ginger, rather the consumption of ginger results in significant decrease in plasma GPT levels as compared to hypercholesterolemic and control groups. The results of present study indicate that Lovastatin is more effective in treating hypercholesterolemia as compared to ginger. On the other hand ginger alone cannot be used effectively for secondary prevention trials, but for primary prevention trials due to adverse effects of Lovastatin on liver functions it can be used effectively.

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