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Hypolipidemic and antioxidant Potential of Zingiber officinal (Ginger) in Cholesterol Fed Rats

S.M. Ali and G. C. Jain*
Department of Zoology, University of Rajasthan, Jaipur - 302004 (India)
*Correspondence

Abstract: In the present study the effect of 70% ethanolic extract of *Zingiber officinale* Linn. rhizome was evaluated on serum and hepatic lipid profiles of hyperlipidemic rats. Experimental hyperlipidemia was induced by feeding cholesterol (500 mg/kg b.wt./day) suspended in coconut oil for 60 days. Feeding with cholesterol resulted in a significant ($P<0.001$) increase in total cholesterol, triglycerides and phosphotipids levels in serum and liver of rats. Serum LDL-cholesterol was also raised significantly. Serum HDL-cholesterol remained significantly unchanged. Co-administration of *Ginger*at different doses for 60 days significantly prevented the cholesterol induced rise in the levels of all those parameters in serum and liver dose dependently. The amount of cholesterol induced lipid peroxidation was significantly reduced and level of glutathione is significantly improved in Ginger fed groups as compared to cholesterol fed controls($P<0.05$). The results of the present investigation suggest that*Z. officinale*extract possesses hypolipidemic and antioxidant activity and could be beneficial in management of hyperlipidemia.
Key words: *Zingiber officinale,* hypolipidemia, rats.

Introduction

Cardiovascular disease is one of themaincause of morbidity and mortality around the world.(WHO report, 2000) Due to change in dietary habits, life style, dyslipidemia and other factors, there is significant increase in the rate of this disease in our country also (Reddy and Yusuf, 1998; Gupta et al, 2001). Atherosclerosis is the principal contributor to the pathogenesis of myocardial and cerebral infarction. Although, atherosclerosis is a multifactorial disease but elevated plasma concentration of cholesterol, especially in low density lipoprotein (LDL), is recognized as the leading cause of the development of atherosclerosis. Evidences from lipid lowering trials have clearly established that reduction of total cholesterol or LDL-cholesterol is associated with decreased risk of atherosclerosis and coronary heart disease.

Beside high LDL-cholesterol (LDL-c), low levels of HDL-cholesterol (HDL-c) is also considered as important coronary risk factor. There is strong inverse relation between serum HDL-cholesterol or a low LDL-c : HDL-c ratio and risk of coronary artery disease. the HDL-cholesterol fraction is largely implicated in transport and or exchange of cholesterol between tissue and plasma. HDL-cholesterol also takes part in the protection of plasma lipids from per-oxidation.Clinical and experimental studies have suggested that oxidatively modified LDL (ox-LDL) have an important role in the initiation and development of atherosclerosis. The exact mechanism by which modified lipoprotein contribute to the disease progression is still not fully understood. A number of studies have shown that inhibition of such LDL modifications may arrest development of atherosclerotic lesion(Dominiczak, 1998; Wierzbicki, 2005)..

In the last few years, increasing attention has been given to lowering serum cholesterol levels to reduce high rate of coronary heart disease. Overwhelming evidence shows that nutritional factors are of prime importance in preventing and modifying the ongoing atherosclerosis process. Among natural products with hypocholesterolaemic activity are β-carotene, polyphenols, lycopene, flavonoids, cycloartenol, β-sitosterol, sitostanol, saponin, soyabean, protein, indoles, dietary fibers, propionates and polysaccharides. A large number of medicinal plants herbal preparations have shown beneficial effects by virtue of their hypocholesterolemic and antioxidant effects(Wang and Ng, 1999; Fugh Berman, 2000, Anila and Viajyalakshymi, 2002; Dwivedi, 2004)

Traditional medicines are still the mainstay of about 70-80% of the world population, mainly in the developing countries. India and China having a very old and rich traditional folk medicine for centuries, has provided simple but effective remedies to various ailments using plants and their derived compounds (Johri and Zutshi, 1992; Lodheand Bogga,2000; Chan, P. and Tomlinson, 2000)

Ginger is used extensively in Ayurveda the traditional medicine system of India to block excessive clotting, reduce cholesterol and fight arthritis (Johri and Zutshi, 1992; Verma and Bordia 2001). It was therefore, felt that it would be worthwhile to investigate the hypo-cholesterolaemic and antioxidant activity of commonly used spice with medicinal property namely, *Zingiber officinale* in cholesterol fed rats.

Material and Methods

Plant Materials

During present investigations following there plant materials were used to assess hypolipidaemic and anti-lipidperoxidation properties:

Zingiber officinale

Fresh ginger rhizomes were purchased from the local vegetable market in Jaipur and authenticated by Department of Botany, University of Rajasthan, Jaipur. (Herbarium sheet no. - RUBL 19825).The rhizomes were dried in the shade, powdered mechanically and extracted with 70% ethanol for 36 hours at 60-80º c. The extract was concentrated at low temperature and reduced pressure. A crude semisolid residue was obtained and suspended in appropriate volume of distilled water to prepare desired concentration for use.

Cholesterol powder

Cholesterol powder was purchased from Merck, India Ltd. and it was dissolved in coconut oil.

Animals

Colony bred healthy, adult male albino rats (Wistar strain) weighing 175-225 g., were used in the present study. The rats were housed in polypropylene cages under controlled conditions of temperature (24 ± 38) and light (12 h light/dark cycle). They were provided with a nutritionally adequate standard laboratory diet (Lipton, India Ltd.) and tap water *ad libitum*.

Experimental design

The rats were randomly divided in to following groups each having 7 rats.

Group I : Rats fed on normal pallet diet

Group II : Rats orally fed with cholesterol (500mg/kg b.wt./ day) dissolved in coconut oil and also distilled water (0.5 ml/ rat). There served as cholesterol fed controls.

Group III : Rats were orally fed with cholesterol (500mg/kg b.wt./day) + *Zingiber officinale* 70% ethanolic crude extract (100mg/kg b.wt./day) suspended in distilled water (0.5 ml/ rat).

Group IV : Rats were orally fed with cholesterol (500mg/kg b.wt./day) + *Zingiber officinale* extract (250mg/kg b.wt./day) suspended in distilled water (0.5 ml/ rat).

Group V : Rats were orally fed with cholesterol (500mg/kg b.wt./day) + *Zingiber officinale* extract (500 mg/kg b.wt./day) suspended in distilled water (0.5 ml/ rat).

All the rats received treatment for 60 days duration.

At the end of experiments, after overnight fasting, rats were sacrificed under mild ether anaesthesia. Blood samples were collected and allowed to clot at 37º c and the serum was separated by centrifugation and stored at 20º c until assayed.

Liver and aorta, were quickly removed, cleaned, washed in cold normal saline and weighed on electric balance. Half of the tissues were fixed in Bouins fixative and aorta was fixed in 10% formo- calcium solution for histological studies. The remaining halves of the tissues were immediately frozen (at -20° / -70ºC) for biochemical analysis.

Biochemical Analysis

Serum parameters

The pooled serum samples were analysed for following parameters -

(i) Total cholesterol (Zlatkis*et al.*, 1953);

(ii) Phospholipids (Zilversmit and Davis, 1950);

(iii) Triglycerides (Gottfried and Rosenberg, 1973);

(iv) HDL-cholesterol (Burnstein*et al.*, 1970);

Altherogenic index was calculated from the following formulae-

$$\text{Atherogenic Index} = \frac{\text{HDL-cholesterol}}{\text{Total cholesterol}}$$

Tissue Biochemistry

Frozen tissue samples were used for the measurements of following parameters :

(i) Total Cholesterol (Liver and Aorta) (Zlatkis*et al.*, 1953);

(ii) Triglycerides (Gottfried and Rosenberg, 1973);

(iii) Phospholipids (Zilversmit and Davis, 1950);

Lipid peroxidation and Antioxidant defense system

Fresh tissues (liver and aorta) of rats were used for the enzymatic parameters on the same day of autopsy.

(1) Lipid peroxidation (TBARS) (Okhawa*et al.,* 1979);

(2) Glutathione (Morron*et al.*,1979);

Statistical Analysis

All the results were expressed as plus animus error. The formula is

Where n = number of observations

E = sum of the observation values

x = variables

The data were analysed for statistical significance by student's 't' test

M1 = Mean of first observations

M2 = Mean of second observations

E1 = Error of first observations

E2 = Error of second observations

Significance 'P' value low significant

$P < 0.01$ modularity significant

$P < 0.01$ highly significant

Observations and Results

Serum Biochemistry

Cholesterol (Fig. 1A)

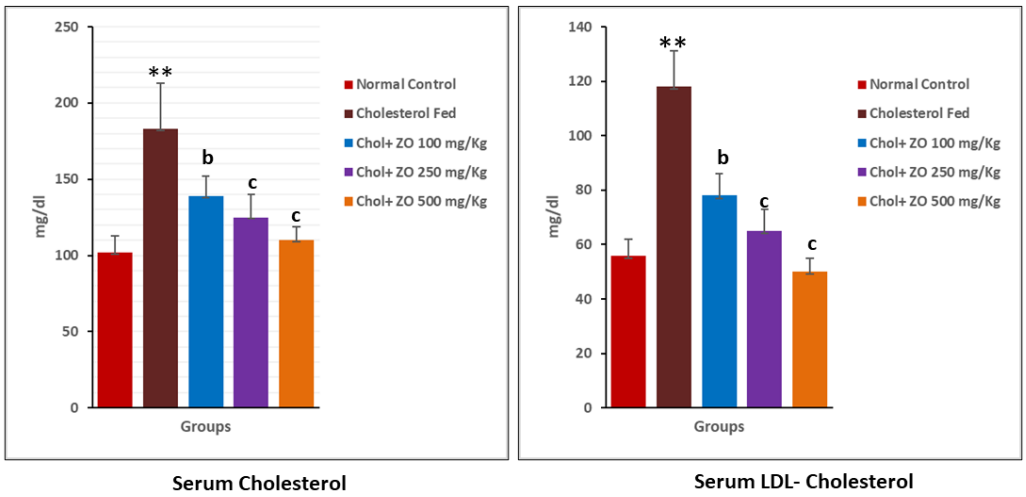
Feeding of cholesterol for 60 days to rats caused 70.82% (P<.001) increase in total serum cholesterol, when compared with normal rats (normal = 108.72 ± 6.66 mg/dl; cholesterol fed control = 185.74 ± 5.70 mg/dl).

Administration of *Zingiber officinale* extract concomitantly with cholesterol significantly prevented the rise in serum cholesterol as compared cholesterol alone fed control rats. The reduction observed at 100, 250 and 500 mg/kg b.wt./day dose levels were -21.51% (P<0.01), -30.73% (P<.001) and -37.67% (P<.001) respectively.

LDL-cholesterol (Fig. 1B)

The level of serum LDL-cholesterol in rats treated with cholesterol was elevated significantly (P<.001) when compared with normal rats.

Feeding of *Zingiber officinale* extract (100 mg/kg b.wt./day) along with cholesterol exhibited a moderately significant (P<.01) reduction in the concentration of serum LDL-cholesterol. Whereas, high doses (250 and 500 mg/kg b.wt./day) caused highly significant (P<.001) decline in serum LDL-cholesterol. The maximum lowering of LDL-cholesterol (-56.70) was seen in 500 mg/kg b.wt./day dose group.



Serum Cholesterol **Serum LDL- Cholesterol**

Compared with Normal: ***=p ≤ .001, **=p ≤ .01, *=p ≤ .05
Compared with Cholesterol fed a=p ≤ .05, b=p ≤ .01, c=p ≤ .001

Figure 1 A and B: Changes in Serum Cholesterol and LDL Cholesterol after administration of Zingiber officinale rhizome extract at given concentrations

HDL-cholesterol / Total-cholesterol Ratio (Fig. 2)

Ratio of HDL-cholesterol / Total-cholesterol was very much reduced in cholesterol fed control. Administration of *Zingiber officinale* extract (100 mg/kg b.wt./day) along with cholesterol exhibited improved the ratio of HDL-cholesterol / Total-cholesterol in a dose dependent manner.

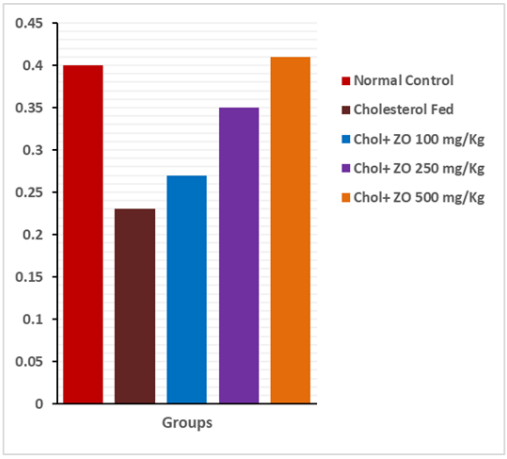


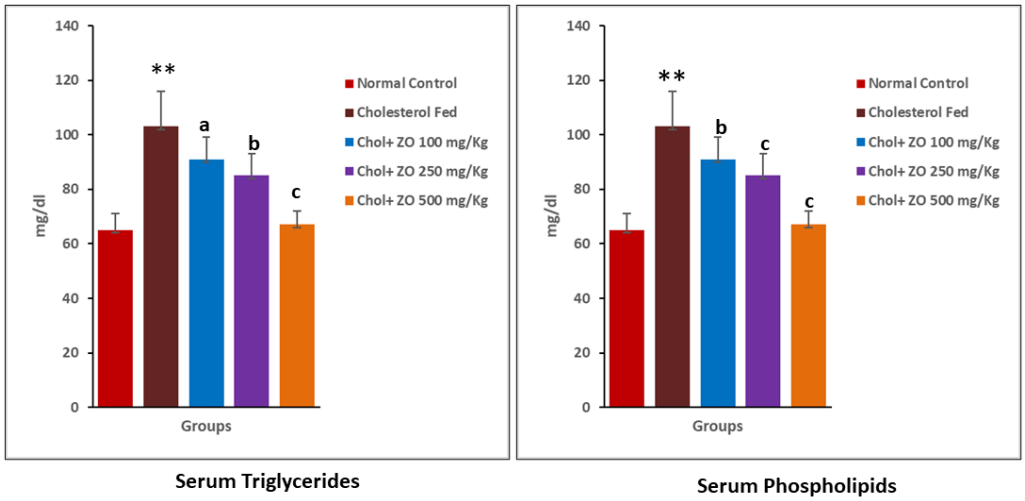
Figure 2: Changes in Serum HDL to LDL Cholesterol ratio after administration of Zingiber officinale rhizome extract at given concentrations

Triglycerides (Fig. 3A)

Serum triglycerides level in rats showed significant (P<.001) elevation following administration of cholesterol for 60 days. Feeding of *Zingiber officinale* extract (100, 250 and 500 mg/kg b.wt/day) along with cholesterol in rats caused significant dose dependent decline (P<.05 to P<.001) in serum triglycerides as compared to cholesterol fed control rats.

Phospholipids (Fig. 3B)

As compared to normal rats, cholesterol fed rats showed 44.35% increase (P<.001) in serum phospholipids concentration.The increase was significantly lowered (P<.01). in *Zingiber officinale* 100 mg/kg b.wt./day + cholesterol fed group. High doses (250 and 500 mg/kg b.wt./day) of *Zingiber officinale* along with cholesterol caused highly significant (P<.001) decline the level of serum phospholipids in rats when compared with cholesterol alone treated rats.



Compared with Normal: ***=p ≤ .001, **=p ≤ .01, *=p ≤ .05
Compared with Cholesterol fed a=p ≤ .05, b=p ≤ .01, c=p ≤ .001

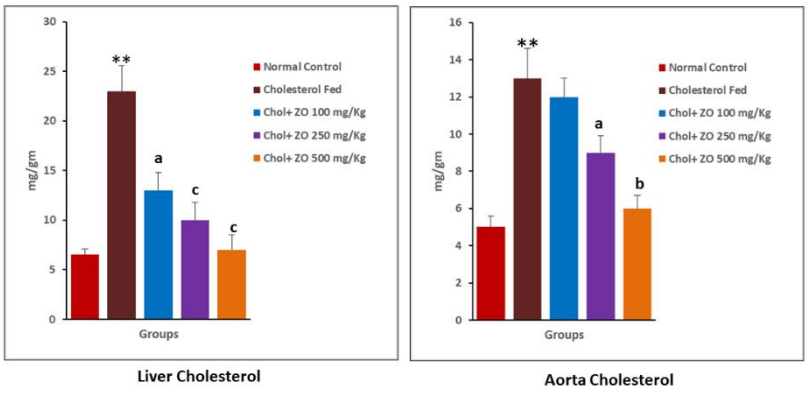
Figure 3 A and B: Changes in Serum Triglycerides and Phospholipids after administration of Zingiber officinale rhizome extract at given concentrations

Tissue Biochemistry

Biochemical changes observed in tissues (liver and aorta) after various treatments are as follows:

Cholesterol (Fig. 4A and B)

Highly significant (P<.001) increase in cholesterol contents of liver and aorta was seen after cholesterol feeding in rats as compared to normal group. Administration of *Zingiber officinale* rhizome extract (100 mg/kg b.wt./day) simultaneously with cholesterol significantly decreased liver (P<.05) and aortic cholesterol (P<.01) values. This decrease in hepatic and aortic cholesterol was highly significant in rats receiving higher doses (250 and 500 mg/kg b.wt./day) of *Zingiber officinale* extract treatment.



Compared with Normal: ***=p ≤ .001, **=p ≤ .01, *=p ≤ .05
Compared with Cholesterol fed a=p ≤ .05, b=p ≤ .01, c=p ≤ .001

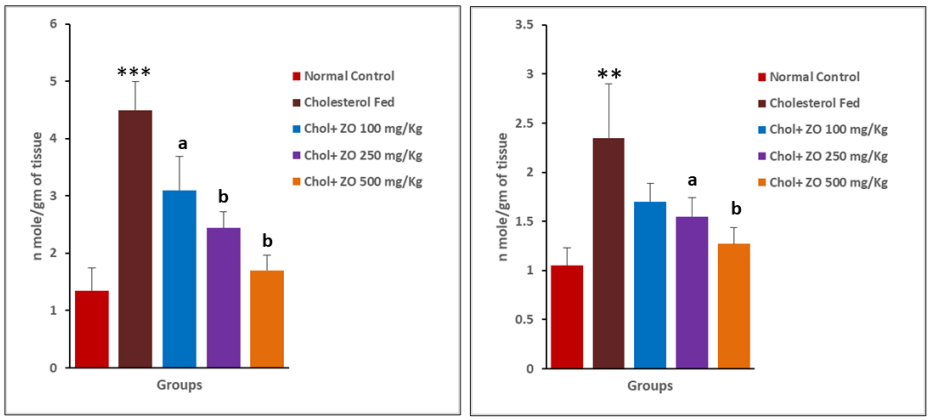
Figure 4 A and B: Changes in Liver and aortic Cholesterol after administration of Zingiber officinale rhizome extract at given concentrations

Antioxidant parameters

Lipid peroxidation (TBARS) (Fig. 5A and 5B)

The quantitative measurement of lipid peroxidation was done by measuring the concentration of thiobarbiteuric acid reactive substances (TBARS).

Cholesterol feeding for 60 days to rats caused significant increase in liver (P<.001) and aortic (P<.01) levels (TBARS).Administration of *Zingiber officinale* rhizome extract (100, 250 and 500 mg/kg b.wt./day) along with cholesterol caused significant dose dependent (P<.05, P<.01, P<.001) decrease in value of lipid peroxides (TBARS) in liver. At 250 and 500 mg/kg b.wt./day doses there was significant (P<.05, P<.01 respectively) decline in aortic lipid peroxides (TBARS) as compared to control rats. However, in low dose *Zingiber officinale* extract (100 mg/kg b.wt./day) treated rats the decrease was non-significant.



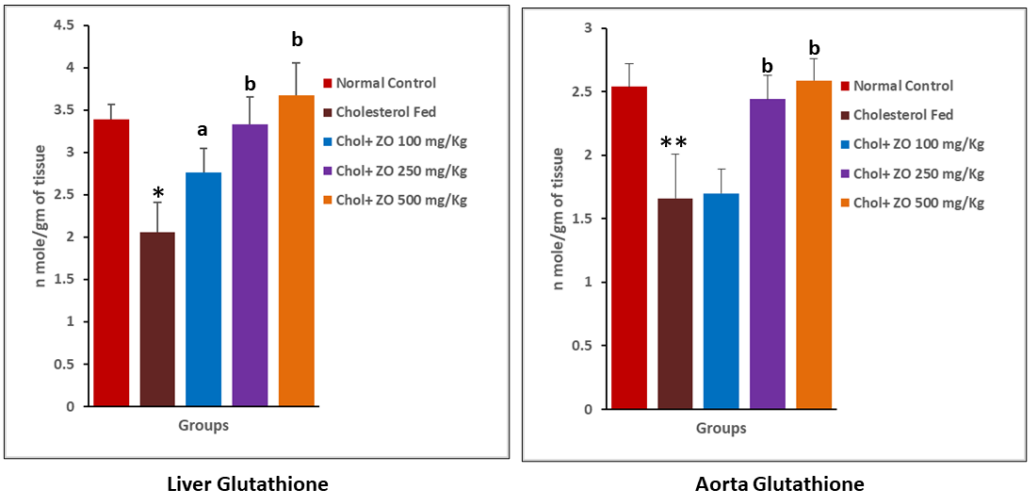
Compared with Normal: ***=p ≤ .001, **=p ≤ .01, *=p ≤ .05
Compared with Cholesterol fed a=p ≤ .05, b=p ≤ .01, c=p ≤ .001

Figure 1 A and B: Changes in Liver and aortic TBARS after administration of *Zingiber officinale* rhizome extract at given concentrations

Glutathione (GSH) (Fig. 6A and 6B)

Oral feeding of cholesterol alone in rats caused significant decrease in glutathione contents of liver (P<.01) and aorta (P<.05) when compared with normal group.Administration of *Zingiber officinale* extract (100 mg/kg b.wt./day) along with cholesterol, showed slight significant (P<.05) increase in the content of glutathione in liver and aorta of rats. High doses of *Zingiber officinale* extract (250 and 500 mg/kg b.wt./day) along with cholesterol registered a moderately significant (P<.01) elevation in both liver and

aortic glutathione levels.



Liver Glutathione Aorta Glutathione

Compared with Normal: ***=p ≤ .001, **=p ≤ .01, *=p ≤ .05
Compared with Cholesterol fed a=p ≤ .05, b=p ≤ .01, c=p ≤ .001

Figure 6A and 6B: Changes in Liver and aortic glutathione after administration of *Zingiber officinale* rhizome extract at given concentrations

Discussion

Atherosclerosis is a multifactorial disease associated with different risk factors. However, hypercholesterolemia especially LDL-cholesterol is a major risk factor for atherosclerosis, which leads to cordiovascular disease (**Hornbtra***et al.*, 1998; Dominczak, 1998). Increased intracellular generation of reactive oxygen species has been proposed a mechanism of tissue injury in a variety of pathological processes including inflammation, ischaemia, reperfusion injury, atherosclerosis and thrombotic diseases (Uday*et al.*, 1999).Epidemiological studies have shown that high intake of fresh fruits and vegetables are associated with lowered risk of coronary heart disease (Hertog*et al.*, 1995). Dietary plant compounds alter cholesterol level by several mechanisms including inhibition of cholesterol absorption, inhibition of cholesterol biosynthesis, increased excretion of bile acids, and by modulating various lipid metabolic enzymes (Romero *et al*, 2002)

In the present investigation administration of *Zingiber officinale* rhizome extract (70% alcoholic) in cholesterol treated rats significantly lowered serum, hepatic and aortic lipid levels. Further these plants also significantly reduced the oxidative stress (TBARS) induced by cholesterol feeding and improved antioxidant defence system in liver and aorta. Thus, the results of present investigation demonstrate strong hypolipidaemic and antioxidative effects of *Zingiber officinale* rhizome extract.

Zingiber officinale extract along with cholesterol significantly lowered the serum total and LDL-cholesterol and concomitantly with a non-significant increase in HDL concentration. Different doses of ginger extract also improved the HDL-cholesterol : total cholesterol ratio in rats. In parallel to our findings Ahmed and Sharma (1997), also reported that supplementation of ginger (0.5%) in diet to rats induced a significant decrease in serum total and LDL cholesterol. It also caused significant elevation in HDL-cholesterol levels.

Connell(1970), also found that administration of ginger oleoresin (1%) causes lowering of serum cholesterol in hypercholesterolemic effects.

An active principle (E)- 8 β, 17 - epoxylavd - 12 - ene - 15,16 dial (ZT), isolated from *Zingiber officinale* rhizome, has been reported to inhibit HMG co. A reductase enzyme activity in rats and mice suggesting inhibition of cholesterol biosynthesis. From the above information it can be concluded that *Zingiber officinale* may lower serum cholesterol either by inhibiting cholesterol biosynthesis in liver or increasing bile acid secretion and faecal bile acid excretion.

Rats treated with different doses of *Zingiber officinale* extract along with cholesterol showed significant dose dependent decrease in serum triglycerides concentration. These results are parallel with Bhandari*et al.,* (1998), who also observed that administration of alcoholic extract of ginger (200 mg/kg p.o.) for 10 weeks significantly reduced serum triglycerides in rabbits fed high cholesterol diet. In contrast to our finding, Ahmed and Sharma (1997), found no significant effect on serum triglycerides level in male rats when administered 0.5% ginger in diet.

Consistent to our results, significant reduction in serum phospholipids were also obtained by Sharma *et al.,* (1996) and Bhandari *et al.,* (1998), after administration of ginger extract for 10 weeks in high cholesterol diet fed rabbits.This reduction of phospholipids in serum may be due to ameliorating effects of ginger or its active constituents on the metabolism of very low density lipoproteins

The generation of reactive oxygen species (ROS) beyond the antioxidant capacity of a biological system give rise to oxidative stress. Free radical oxidative stress has been implicated in the pathogenies of a variety of human diseases including atherosclerosis.

In the present study, significant increase of TBARS activity in liver and aorta was observed in cholesterol fed (control) rats. Elevated TBARS in cholesterol fed group suggests the enhanced oxidative stress in hyperlipidaemic state as represented by earlier studies in liver (Lu and Chiang, 2001; Ferre*et al.,* 2001), and aorta.Rise in TBARS considered to be the indicator of the onset of oxidative stress from reduced species of molecular oxygen in including hydrogen peroxide, superoxide radicals and reactive hydrogen radicals.

Administration of *Zingiber officinale* extract along with cholesterol caused significant reduction the levels of TBARS in liver and aorta indicating antilipid peroxidative nature of *Zingiber officinale* extract. These results are in agreement with the results obtained by Ahmed *et al.,* (2000), who also observed that concomitant dietary feeding of ginger (1% w/w) for four weeks significantly lowered hepatic lipid peroxidation by maintaing the activities of antioxidant enzymes in rats.

Glutathione is a predominant tripeptide thiol compound (γ- glutamyl cysteinyl glycine, GSH), is synthesized in liver from its precurors amino acids eg.γ- glutamate, cysteine and glycine. Liver translocates GSH to the blood plasma and to the bile. Glutathione is mainly involved in detoxification mechanism through conjugation reactions. Other functions include thiol transfer, destination of free radicals and metabolism of various exogenous and endogenous compounds. It becomes modulatory for a cell to manage high concentration of intracellular GSH to protect self from chemical / drug abuse.

The results of present study showed that administration of cholesterol dissolved in coconut oil for 60 days caused significant decrease in the level of glutathione in liver and aorta of rats. This significant decrease of GSH in in cholesterol fed rats might be due to the enhanced oxidative stress in hyperlipidaemic state as reported by earlier studies in liver (Dhuley, 1999; Lu and Chiang, 2001;) and aorta (Dhuley, 1999)). Simultaneous administration *Zingiber officinale* extract with cholesterol caused significant increase in the level of liver and aortic glutathione levels in rats. These findings are parallel with the finding of Jeykumar*et al.*, (1999), who showed that supplementation with ginger to high fat fed animals significantly elevated the level of glutathione in liver.

It can be concluded that ginger extract inhibit lipid peroxidation significantly and recovered the decreased hepatic GSH level induced by cholesterol therapy.The present study, indicates that the rhizome of *Zingiber officinale*, contain biologically active components that may prevent atherosclerosis risk by lowering serum cholesterol and lipid peroxidation effectively. It is also effectively enhance the serum HDL/LDL cholesterol ratio and Needless to say, further extensive research is suggested for isolation, identification and evaluation of their active principle(s) in order to develop a hypolipidaemic agent of natural origin.

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