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Full Length Research Paper

An experimental study to evaluate the preventive effect of *Zingiber officinale* (ginger) on hypertension and hyperlipidaemia and its comparison with *Allium sativum* (garlic) in rats

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Hypertension and hyperlipidemia are the two most important risk factors associated with high incidence of adverse coronary events and the incidence is increasing very rapidly specially in developing countries due to adoption of faulty eating habits and physical inactivity. In this study, we have focused mainly on two objectives. The first one is to provide safer, natural and effective alternative remedy against these risk factors because no drug in the modern medicine is devoid of the side effects and the second objective is to prevent the generation of risk factors rather than the treatment of the same because prevention is always better than cure. In this study, we have explored the preventive effect of ginger on blood pressure and lipid profile in rats fed on high fat diet (HFD) and comparison was done with the preventive effect of another natural herb garlic, which is a more studied and established herb against these risk factors. Total 18 rats were taken and divided equally into three (control, ginger and garlic) groups by random selection. Ginger and garlic (500 mg/kg orally) were given to two separate groups of rats fed on high fat diet for a period of 7 weeks. Blood pressure and lipid profile were measured on day 0 and after 7 weeks. Blood pressure was measured with the help of NIBP machine and the measurement of lipid profile blood sampling was done by intracardiac route. In this study, ginger have shown significant ($p < 0.01$) preventive effect on systolic blood pressure and lipid level in comparison to control group. Ginger have not shown significant ($p > 0.05$) increase in high density lipoprotein (HDL) level in comparison to control. Comparative study with garlic have shown that ginger has better although not significant preventive effect on systolic blood pressure and garlic has better preventive effect on lipid levels. On the basis of the aforementioned results, we can conclude that ginger like that of garlic may act as a better natural and safer alternative in the prevention of adverse coronary events and their risk factors like hypertension and hyperlipidemia.

Key words: Ischemic heart disease, hyperlipidemia, hypertension, ginger, garlic, total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein.

INTRODUCTION

Both clinical and epidemiologic studies have shown that hyperlipidemia and hypertension are perhaps the major risk factors of atherosclerosis and its complications, such as stroke and Ischemic heart disease (IHD) which leads to myocardial infarction (Hulley et al., 1980; Ridker and Libby, 2005). There is evidence that long-term, effective treatment of hyperlipidemia and hypertension can decrease the occurrence of ischemic heart disease (Downs et al., 1998; Scandanavian et al., 1994; Shepherd et al., 1995; Sacks et al., 1996; Kleijnen et al, 1989).

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A wide variety of therapeutic agents in modern medicine are available against these diseases like antihypertensives (Angiotensin converting enzyme inhibitors, beta blockers, diuretics, calcium channel blockers etc.) and anti hyperlipidemics (statins, fibrates, resins etc.) but most of these drugs are having potentially serious side effects and high cost, and if therapy is not regularly monitored can lead to toxicity and noncompliance. Most of these drugs are not suitable to be used as a preventive measure against these risk factors.

Apart from the aforementioned pharmacological measures, there is continuous search for alternative treatment of hypertension and hyperlipidemia; therefore it is evident to look for options and switch on to more safer indigenous system of medicine like natural herbs as WHO (1980) has also recommended the evaluation of the effectiveness of plants in conditions where no safe modern drugs are available (Upadhaya and Pandey, 1984). A number of herbal products had claimed the beneficial effect on risk factors of cardiovascular disease in terms of hypertension and hyperlipidemia which ultimately leads to ischemic heart disease. Some common examples are *Allium sativum*, Green tea, *Terminalia arjuna, Zingiber officinale, Withania somnifera, Commiphora mukul /wightii, Panax ginseng* and *Ginkgo biloba*.

However, most of the studies are based on exploring the curative effect rather than the preventive effect on risk factors of ischemic heart disease like hypertension and hyperlipidemia which have received very little attention. In view of this deficiency, the present work was undertaken in order to investigate the preventive effects of ginger on blood pressure and serum lipid profile, namely total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) in rats fed on high fat diet (HFD), and comparison was done with relatively more tested herbal drug, that is, garlic (Omran, 2006; Sanjay and Maulik, 2002).

MATERIALS AND METHODS

Animals

Adult healthy Wistar rats of either sex, weighing 140 to 150 g were used in the present study. Animals were procured from CPCSEA certified animal house (IITR, Lucknow). They were given food (10% high fat diet) and water *ad libitum* and were kept in Institutional animal house under temperature, humidity and light and dark cycle controlled environment [25 ± 2°C, 70%, 12 h cycle). Care of animals was taken as per guidelines of the committee for the purpose of control and supervision of experiments on animals. The experimental protocol was approved by the institutional ethics committee.

Test drugs

Ginger (*Z. officinale*) dried powder preparation was administered in a dose of 500 mg/kg (Xianglu et al., 2009). Ginger was procured from IITC Organic India, Lucknow. Capsules of garlic (*A. sativum*) of same batch containing garlic powder was procured from Himalaya drug company, Bangalore and administered orally in a dose of 500 mg/kg (Omran et al., 2006; Thompson et al., 2009). All the drugs were given orally with the help of feeding cannula after suspension in distilled water.

We have chosen the most effective dose, that is, 500 mg/kg (in reference to the few of the previous studies done so far) for this preventive study and will further do the experimental and clinical dose response studies if this found to be effective .

In the present study, we have used garlic as a reference drug as it is the most scientifically tested herb against these risk factors and also prescribed for long time as a an alternative medication for these risk factors especially hyperlipidemia. Moreover, most of the regular allopathic medicines are not suitable as preventive measures as they have various side effects and can produce toxicity on long term use in a healthy person (they are mostly used in a patient who has already developed these risk factors).

High fat diet (HFD) was prepared by Dayal Industries Pvt. Limited, Barabanki Road, Lucknow (Uttar Pradesh), India. Ingredients were as follows: Crude fat (15%), crude protein (16%), acid insoluble ash (2.5%), moisture (8%) and vitamins and minerals in appropriate quantity.

Experimental protocol

A total number of 18 Wistar rats were included in the study. The weight of all rats was taken before starting the study. All rats were fed with high fat diet for 7 weeks to induce hypertension and hyperlipidemia (Anca et al., 2000; Gordan et al., 1986). Base line systolic blood pressure (SBP) was recorded on day 0 and simultaneously blood sample was drawn to measure baseline lipid levels. Rats were divided randomly in to three groups.

Group 1 (Control group): In control group (n=6) only high fat diet (HFD) was given for a period of 7 weeks
Group 2 (Ginger group): In Ginger group (n=6), ginger was given along with HFD in a dose of 500 mg/kg for 7 weeks
Group 3 (Garlic group): In garlic group (n=6), garlic was given along with HFD in a dose of 500 mg/kg for 7 weeks.

After 7 weeks, systolic blood pressure and lipid profile were measured to see the preventive effect of ginger and garlic on hypertension and lipid level and statistical analysis was done between ginger, garlic and control groups.

Measurement of systolic blood pressure (SBP)

SBP was measured by tail cuff method with the help of NIBP Controller Machine [ML125] AD Instruments (Australia).

Biochemical analysis in blood

Blood sample of 1.5 ml volume was taken by intracardiac route for chemical analysis and serum was separated with the help of centrifuge at a rate of 4000 rpm for 10 min.

Estimation of lipid profile

Lipid profile was measured with the help of semi autoanalyser (Roche company) and Infinite Kit (Accurex Biomedical Pvt. Ltd.) was used for plasma lipid estimation.

Table 1. Baseline systolic blood pressure and lipid profile summary (Mean ± SD) in rats of three groups.

Variable	Control (n=6)	Ginger (n=6)	Garlic (n=6)	F value (2,33 DF)
SBP	109.42 ± 5.70	108.83 ± 5.04	108.50 ± 5.58	0.079^{ns}
TC	37.28 ± 2.67	36.85 ± 2.13	37.57 ± 2.11	0.125^{ns}
TG	29.38 ± 2.66	29.85 ± 2.37	30.35 ± 2.46	0.370^{ns}
HDL	15.50 ± 2.46	15.47 ± 2.28	15.78 ± 2.10	0.038^{ns}
LDL	16.53 ± 2.86	16.87 ± 2.56	16.35 ± 2.48	0.056^{ns}

ns, p>0.05.

Estimation of total cholesterol (TC) in serum

Infinite liquid cholesterol reagent is used for the determination of TC based on enzymatic method using cholesterol esterases, cholesterol oxidase and peroxidase.

Estimation of (triglycerides) TG level in serum

Infinite liquid triglycerides reagent is used for the determination of TG based on enzymatic method using lipoprotein lipase, glycerol kinase, glycerol phosphate oxidase and peroxidase.

Estimation of high density lipoprotein (HDL) level in serum

HDL cholesterol precipitating reagent is used in conjunction with cholesterol reagent for enzymatic determination of HDL in serum.

Estimation of LDL using the Fried Wald formula

LDL-C = (TC) - (HDL-C) - (TGs/5)

Statistical analysis

The data was analyzed by two way repeated measures ANOVA using general linear models (GLM) and the significance of mean difference between groups were done by Newman-Keuls post hoc test and $p<0.05$ was considered statistically significant. All values were expressed as mean ± SD. Analyses were performed on STATISTICA (version 6.0).

RESULTS AND DISCUSSION

Basal study

The baseline (basal or pretreatment) systolic blood pressure (SBP) and lipid profile (TC, TG, HDL and LDL) of three groups (control, ginger and garlic) of rats are summarized in Table 1 and also shown graphically in Figure 1a to e.

Preventive study

The basal (at 0 week) and preventive (at 7 week) systolic blood pressure (SBP) and lipid profile (TC, TG, HDL and LDL) of three groups (control, ginger and garlic) of rats are summarized in Table 2 and also shown graphically in Figures 1a to 1e.

Between groups

Table 2 showed that the levels of SBP, TC, TG, HDL and LDL increased in all three groups after 7 weeks (preventive) as compared to 0 week (basal) due to the effect of high fat diet.

Within groups

The significance of mean difference of SBP, TC, TG, HDL and LDL within the three groups of preventive (after 7 week) are summarized in Table 2a.

DISCUSSION

The present study was done to see the preventive effect of the herb, ginger on two major risk factors of coronary artery disease (CAD), that is, hypertension and hyperlipidemia. These effects were compared with another herb garlic which is a more tested and established herb against these risk factors and taken as a reference drug.

The present study have shown good preventive effect of ginger on hypertension and hyperlipidemia as the increase in blood pressure an d lipid levels is lower in preventive ginger group than control group and which is statistically significant .

Ginger (*Z. officinale*) is one of the most popular of all the spices and it is also one of the top five antioxidant foods (American Journal of Clinical Nutrition, July 2006) (Scott, 2010). Ginger is now considered much existing interest for its potential to treat many aspects of cardiovascular disease. Reviews of the more recent trials, suggest that ginger shows considerable anti-inflammatory, antioxidant, anti-platelet, hypotensive and hypolipidemic effect *in vitro* and animal studies (Nicoll and Henein, 2009). Should these prove positive, ginger has the potential to offer not only a cheaper natural

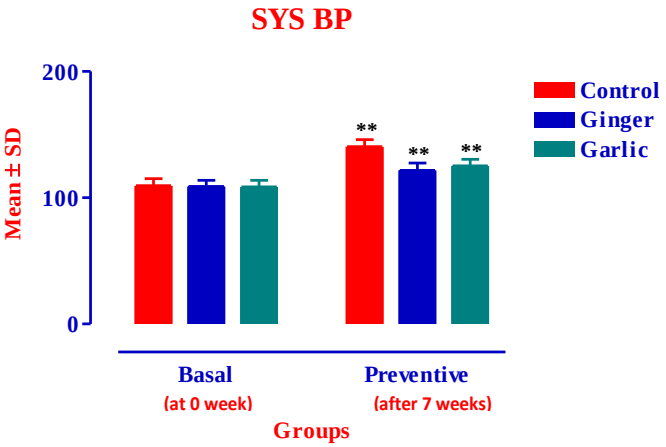

Figure 1a. Bar graph showing comparative systolic blood pressure (mm Hg) mean (± SD) in three groups of rat of basal and preventive study. **, p<0.01 (highly significant).

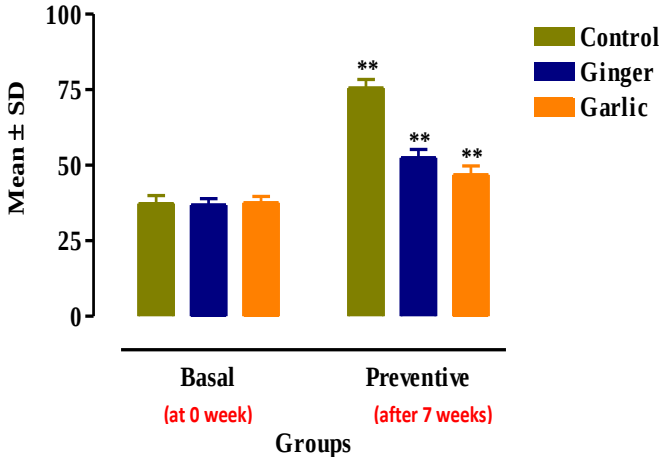

Figure 1b. Bar graphs showing comparative total cholesterol (TC) mean (± SD) in the three groups of rat of basal and preventive study. **, p<0.01 (highly significant).

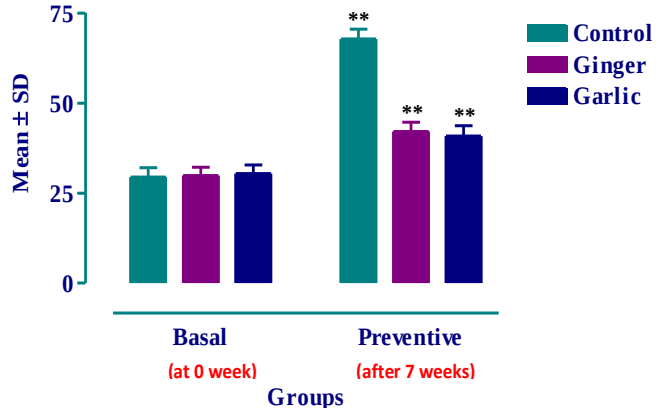

Figure 1c. Bar graphs showing comparative and triglyceride (TG) levels mean (± SD) in the three groups of rat of basal and preventive study. **, p<0.01 (highly significant).

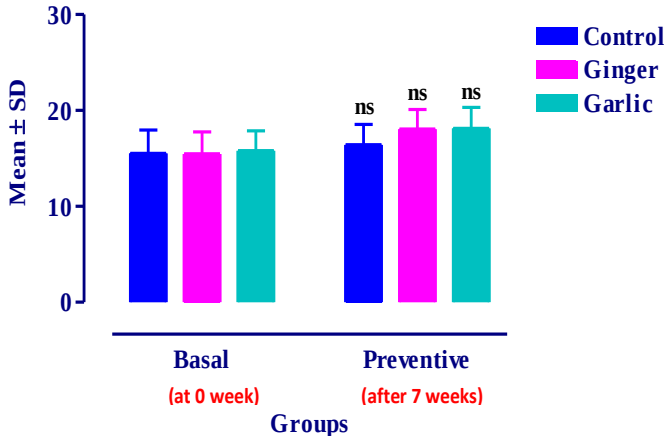

Figure 1d. Bar graph showing comparative high density lipoprotein (HDL) mg/dl levels mean (± SD) in three groups of rat of basal and preventive study. ns, p>0.05 (not significant), **, p<0.01 (highly significant).

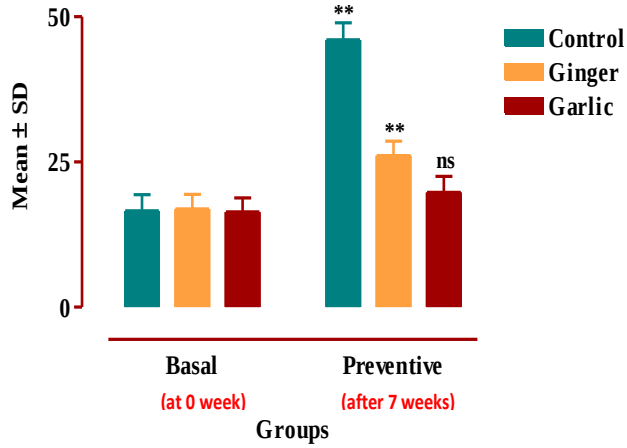

Figure 1e. Bar graph showing comparative low density lipoprotein (LDL) mg/dl levels mean (± SD) in three groups of rat of basal and preventive study. . ns, p>0.05 (not significant), **, p<0.01 (highly significant).

alternative to prevent and to treat these risk factors but one with significantly lower side effects.

Ginger rhizome chemically, contains several classes of compounds including starch (40 to 60%), proteins (10%), fats (10%), fibers (5%), inorganic material (6%), moisture (10%) and essential oil (1-4%). The essential oil (oleoresin) of ginger contains various terpins and sesquiterpenes (Zingiberene). In all, more than 200 different volatile substances have been characterized in the essential oil fraction. The characteristic pungent odor is due to its oleoresin content, which is an oily liquid containing oxymethyl phenols like shagoal, zingerone and gingerol (Verma et al., 1999). Gingerol and Shagoal though considered the main active principle , ginger may not truly represent the crude extract in all aspects because single plant is known to contain as many as over

100 chemicals (Harborne, 1984), therefore in our present study we have used purified dried powder of ginger (Standardized by Organics India). Moreover it is the safest form to consume as drug in future as compared to various other forms inclusive of extracts.

Preclinical safety profile of ginger

Adverse effect associated with ginger are mild which include heart burn, gastric irritation and allergy. Alcoholic extract are said to be more cytotoxic than non alcoholic ginger extract or powder which we have used in our present study (Churabasic et al., 2005).

The acute oral LD50 of ginger oil in rats exceeds 5 gm/ kg and 80% ethanol extract of ginger at 2.5 gm/ kg is not lethal (Chrubasic et al., 2005). Therefore 500 mg / kg (75 mg/ 150 gm rat) dose used in present study is safe for human studies and also for preventive and curative treatment of hypertension and hyperlipidemia in patients.

We have chosen the oral route for giving the herbs as a drug, as this route is natural and usual route of taking these herbs in our diet. One can take these herbs easily by this route if found effective in hypertension and hyperlipidemia .

We have taken three major groups of rats (n=36) in our present study.

Basal values of systolic blood pressure and lipid levels in all three major groups, that is, Group I (control, n=6), Group II (Ginger group, n=06) and Group III (Garlic group, n=06) have shown no significant change and were almost similar to each other (Table 1 and Figure 1a to e) .

Hypertension and hyperlipidemia were experimentally produced by giving high fat diet (HFD) for 7 weeks (Anca et al., 2000; Gordan et al., 1986) to all the three major groups of rats. The HFD was continued for another 4 weeks in control group to see any further changes in parameters but it did not show any significant change. It shows that 7 weeks of HFD is sufficient to produce hypertension and hyperlipidemia. There was also mean 20% increase in body weight of rats in control group from the basal levels after taking HFD; this also strengthens the role of high fat diet in producing these risk factors.

Results have shown significant increase (having +22% change from basal level, $p < 0.01$) in systolic blood pressure in control group after 7 weeks of daily high fat diet along with significant increase in lipid levels from the basal values (Total cholesterol- +50.6%, triglyceride- +56.6% and LDL- +64.1%, $p < 0.01$). High density lipoprotein (HDL) levels have shown only mild increase which was statistically not significant (Table 2 and Figure 1a to e). These results are in accordance with the previous studies done with high fat diet.

Since we know that prevention is always better than cure of a disease, in this study we have explored the preventive effect of ginger and compared it with garlic.

In the preventive study, the groups have been evaluated for preventive effects of ginger and comparative preventive effects of garlic on hypertension and hyperlipidemia. Results have shown that the group which was given ginger exhibited significant increase in blood pressure (BP) after taking high fat diet and the group of rats which were given only high fat diet, that is, control group has also shown significant increase in BP as mentioned previously. Thus we can see from these results that in preventive group of ginger treated rats, there was significant increase in systolic BP but it was significantly (change from control group was -13.4% , $p < 0.01$) less than that of control group (Tables 2 and 3 and Figure 1a) .

The preventive group which was given garlic has also shown significant increase in blood pressure, but the increase in preventive group was significantly less (change was -10.8% , $p < 0.01$) than that of control group as was shown in the preventive group which was treated with ginger. If we see the comparison between ginger and garlic in preventive groups there was no significant difference in increase in systolic blood pressure (only 3% change) , but the ginger group has shown comparatively less increase in BP than garlic group (Tables 2 and 3 and Figure 1a). Ghayur and Gilani (2005) have also shown that ginger has blood pressure lowering effect by blockade of voltage gated calcium ion channels.

The lipid levels in preventive group treated with ginger have shown increase in total cholesterol (TC), triglyceride (TG) and LDL from basal level but only mild increase in HDL level but comparatively there was significant increase in lipid levels in control group which were taken only high fat diet. The change from control group TC (-30.6%), TG (-37.9%) and LDL (-43.3%) was statistically significant ($p < 0.01$) and there was little change in increase in HDL levels from control. But comparatively there was more increase in HDL or good cholesterol in ginger group than in control group (Tables 2 and 3 and Figure 1b to e).

The results of preventive group taking garlic on cholesterol has shown increase in lipid levels which was maximum in LDL and only mild increase in HDL levels like that of ginger group. But comparatively there was less increase in lipid levels than the control group taking only high fat diet (change from control group in total cholesterol was -38%, in triglyceride was -39.8%, in LDL was – 57.1% ,which was statistically significant, $p < 0.01$) and HDL levels have shown only mild change which was not significant. But again like that of ginger group, there was comparatively more increase in good cholesterol from that of control.

Comparative preventive study of lipid levels of ginger and garlic treated groups have shown only mild change in triglyceride and HDL levels but significant change in total cholesterol and LDL levels ($p < 0.01$), that is, there was comparatively less increase in LDL and total cholesterol than ginger group. This shows that preventively garlic is more effective than ginger in controlling lipid levels. The

Table 2. Baseline and after 7 weeks systolic blood pressure (mm Hg) and lipid profile (mg/dl) summary (Mean ± SD) in rats treated with control (n=6), ginger (n=6) and garlic (n=6).

Variable	Groups			Basal vs. preventive	Mean change (%)
	Treatments	Periods			
		Basal (0 week)	Preventive (7 weeks)	Mean difference	
SBP	Control	109.42 ± 5.70	140.25 ± 5.79	30.83**	22.0
	Ginger	108.83 ± 5.04	121.50 ± 5.96	12.67**	10.4
	Garlic	108.50 ± 5.28	125.17 ± 5.31	16.67**	13.3
TC	Control	37.28 ± 2.67	75.53 ± 2.88	38.24**	50.6
	Ginger	36.85 ± 2.13	52.43 ± 2.79	15.58**	29.7
	Garlic	37.57 ± 2.11	46.85 ± 2.95	9.28 **	19.8
TG	Control	29.38 ± 2.66	67.72 ± 2.82	38.35**	56.6
	Ginger	29.85 ± 2.37	42.07 ± 2.63	12.22**	29.0
	Garlic	30.35 ± 2.46	40.78 ± 2.93	10.43**	25.6
HDL	Control	15.50 ± 2.46	16.39 ± 2.14	0.89^{ns}	5.4
	Ginger	15.47 ± 2.28	18.03 ± 2.07	2.57^{ns}	14.2
	Garlic	15.78 ± 2.10	18.13 ± 2.20	$2.35n^{s}$	13.0
LDL	Control	16.53 ± 2.86	46.00 ± 2.98	29.48**	64.1
	Ginger	16.87 ± 2.56	26.07 ± 2.52	9.20**	35.3
	Garlic	16.35 ± 2.48	19.73 ± 2.78	3.38^{ns}	17.1

^{ns}, p>0.05, **, p<0.01.

Table 3. Significance of preventive systolic blood pressure and lipid profile in three rat groups.

Variable	Control vs.				Ginger vs.	
	Ginger		Garlic		Garlic	
	Mean difference	Mean change (%)	Mean difference	Mean change (%)	Mean difference	Mean change (%)
SBP	18.75^{**}	13.4	15.08^{**}	10.8	3.67^{ns}	3.0
TC	23.09^{**}	30.6	28.68^{**}	38.0	5.58^{**}	10.6
TG	25.65^{**}	37.9	26.94^{**}	39.8	1.28^{ns}	3.1
HDL	1.65^{ns}	10.0	1.75^{ns}	10.7	0.10^{ns}	0.6
LDL	19.94^{**}	43.3	26.27^{**}	57.1	6.33^{**}	24.3

^{ns}, p>0.05, **, p<0.01.

proposed mechanisms in various studies done so far for this effect of ginger are as follows:

1. It inhibits the hydroxymethylglutaryl Co A (HMG-Co A) reductase (Tanabe et al., 1993) which is a rate limiting enzyme for cholesterol biosynthesis (like that of statins).
2. It promotes excretion and impairs absorption of cholesterol (Tanabe et al., 1993).

It increases the activity of 7- alphahydroxylase, the rate limiting enzyme in the catabolic conversion of cholesterol to bile acids in liver (Yamahara et al, 1985; Murugaiah et al., 1999) .

Despite the aforementioned studies on mechanism of lowering the cholesterol levels by ginger more studies are needed for the confirmation, that is, whether only one or more of the aforementioned proposed mechanisms are associated with decrease in lipid levels.

The lipid lowering effect in garlic is said to be due to presence of organosulphur compounds and mechanism of lowering of cholesterol is proposed to be due to inhibition of HMG- Co A reductase (Yu and Liu, 2001; Mathew et al., 2003) like that of ginger and some studies have shown that it also increases cholesterol excretion (Chi, 1982) .

May be because of the presence of these compounds e.g. diallyldisulphide (DADS) etc. (Mathew et al , 2003), garlic is more effective in hyperlipidemia in comparison to ginger .

Moreover, the increase in body weight from basal

levels of rats in ginger and garlic groups were 9 and 8%, respectively which was significantly less than that of the control group.

The studies with preventive group taking ginger have shown significant preventive effect of ginger on hypertension and hyperlipidemia. Another preventive group taking garlic have also shown good preventive effect on hypertension which was significant but less in extent than that of ginger and have better preventive effect on hyperlipidemia (except triglyceride and HDL or good cholesterol levels) in comparison to ginger (Table 2 and 3 and Figure 1b to e).

The results of preventive study on ginger are in accordance with the previous literature which shows preventive effect of ginger on cardiovascular disease (Keith, 2010; Colclasure, 2009) but no comprehensive planned study has been done to see the preventive effect of ginger on hypertension only few on hyperlipidemia (Murugaiah et al., 1999), comparatively more preventive studies (Bordia et al., 1982; Banerjee and Maulik, 2002) were done on garlic and they were also in agreement with our present study.

Conclusion

On the basis of the aforementioned results, we can conclude that ginger is an effective herbal remedy for the risk factors (hypertension and hyperlipidemia) of IHD and if taken preventively, it will be very effective in reducing the chances of developing these risk factors. Comparatively, garlic which is more tested against these cardiovascular risk factors have shown superior effect in reducing lipid levels as preventive remedy than ginger, but ginger has an edge over garlic in reducing blood pressure.

So ginger has the potential to provide not only the cheaper and natural alternative but also the effective preventive remedy for the risk factors (hypertension and hyperlipidemia) of ischemic heart disease (IHD) to develop and therefore reducing the chances of developing various cardiovascular disorders with significantly lower side effects.

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