Antioxidant and Hepato-protective effects of Ginger in Comparison with Atorvastatin in Hyperlipidemic Albino mice.

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ABSTRACT:

Objective: This study was aimed to observe the effects of high fat diet on lipid levels and histomorphology of liver and detecting the preventive effects of ginger and atorvastatin on high fat diet induced hyperlipidemia in albino mice. Also the comparison between the two protective agents was observed.

Methodology: This experimental study was conducted at Department of Anatomy and Pathology, LUMHS Jamshoro and Sindh Agriculture University Tando Jam for six months. This research comprised of 60 adult male mice, divided into four groups (each having 15 animals). Group A, normal control was given standard chow while Groups B, C and D were given high fat diet (cheese) along with chow for eight weeks followed by administration of ginger (15mg/30gm) to Group C and atorvastatin (0.3mg/30gms) to Group D for another eight weeks. Animals of Group B, hyperlipidemic control were left untreated. Weight of animals was measured weekly. Samples for serological and histological changes were taken before and after the induction of high fat diet and at the end of experiment.

Results: The research revealed deranged lipid profile with increased total cholesterol, triglycerides, low density lipoprotein cholesterol and Alanine transaminases, decreased levels of high-density lipoprotein cholesterol and distorted hepatic architecture after high fat diet which were significantly improved by the administration of ginger in Group C animals and to a lesser extent by atorvastatin in Group D.

Conclusion: Ginger only or concurrently with drug therapy proved to be effective hypolipidemic, antioxidant, and hepatoprotective agent, reducing the vulnerability to chronic co-morbidities.

Keywords: Atorvastatin; Ginger rhizome; Hepatic ballooning; Lipid profile; Liver; Steatosis.

Introduction:

Hyperlipidemia is of escalating concern worldwide, considering its significant correlation to imbalanced homeostasis of diverse bodily mechanisms.[1] It is a leading factor that aggravates double fold the risk of myocardial infarction, stroke, and premature deaths, can be modified to reduce these catastrophic events.[2] As per World Health Organization (WHO) estimates, hyperlipidemia (hypercholesterolemia) is accountable for 1/ 3rd of cardiovascular and 1/5th of cerebrovascular diseases which parallels 2.6 million deaths annually around the globe.[2,3] Hyperlipidemia is broadly categorized into primary due to genetic defects (Familial Hypercholesterolemia) and secondary rendering to numerous factors such as dietary habits (high consumption of sugars, saturated or trans-fat, alcohol), drugs (thiazide diuretics, hormonal therapies, glucocorticoids, b- blockers) and diseases (hypothyroidism, obesity, type 2 diabetes mellitus, renal, PCOS).[4] High fat diet consumption, sedentary life style with no physical activity, smoking and alcoholism are major contributing factors in the occurrence of hyperlipidemia which if not managed, can lead to severe impairment of vital organs associated with lipid metabolism.[5] Liver is mainly responsible for the metabolism of various biomolecules including lipids.[6] Disruption to physiological cellular activities leads to excessive accumulation and peroxidation of fats and altered morphology of hepatocytes. Diet rich in fats causes abnormal deposition of fatty acids within hepatocytes altering their structural architecture and physiology resulting into excessive permeability of enzymes in the bloodstream.[1] Ginger is aromatic herb, being utilized as folk medicine since ancient times and contains multitudinous range of components which exert many favorable effects on human health. Its antihyperlipidemic property is attributed to chemical compound ZT{[E]-8b,7-epoxylabd-21-ene-15,16-dial that limits HMG-Co-A reductase and enhance cholesterol-7 alpha-hydroxylase and lipases activity.[7] Ginger has niacin responsible for transport of LDL to the liver with reduced generation of cholesterol and triglycerides and effective clearance of VLDL. Ginger contains [6]-gingerol and [6]-shogaol which degenerate Reactive oxygen species (ROS) and inhibit their production by lowering enzyme xanthine oxidase. It acts as hepatoprotective agent by inhibiting lipid peroxidation and reverse structural alterations due to any insult.[8] Other known benefits include antiemetic, analgesic (dysmenorrhea, arthritis)[9] antineoplastic, antihypertensive, antimicrobial, neuroprotective, reno-protective, immune-modulatory and anti-inflammatory responses due to its phenolic compounds.[8] The action of ginger as insulin sensitizer renders its efficacy in Diabetes Mellitus.[7] Statins, of which atorvastatin is highly effective and recommended, are mainstay treatment for hyperlipidemia and prevent risks related to cardiovascular diseases. It controls lipids and lipoproteins by competitive inhibition of HMG-CoA re-

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ductase and also enhances sensitivity to the LDL-c receptors. Statins along with their beneficial effects, have adverse outcomes like liver, gastrointestinal and renal diseases, myalgia, migraine, diabetes mellitus and cataract. Statins also damage architecture of liver and elevate liver enzymes therefore given cautiously to patients with liver diseases.[10] As these allopathic medicines impose hazardous effects, researches are required to ascertain tremendous advantageous role of natural herbal agents as alternate safe treatments with minimum cost burden and adverse outcomes. Therefore, the present research illustrates ginger as effective hypolipidemic, hepatoprotective and antioxidant agent as compared to Atorvastatin on induced hyperlipidemia in male albino mice.

Methodology::

The experimental study was conducted at Animal House, Department of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tando Jam, Department of Anatomy and Department of Pathology, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, from February 2018 to July 2018 after approval from institutional Ethical Review Committee (ERC NO. LUMHS/REC/-630 dated 08/12/2017) and Board of Advance Studies and Research (BASR).

In this study, sixty adult male albino mice (C57BL/6J) were selected with average weight 28-35gms and age 6-8 weeks with exclusion of unhealthy (low weight and diseased) and female mice (due to their hormonal concentrations on different estrous days that can alter effects of preventive drugs). All animals were handled according to the guiding principles by US National Institutes of Health (NIH) and housed in stainless steel cages (with sawdust bedding). The cages were equipped with standard containers and plastic drinkers with nozzles for food and water, respectively. The animals were housed under hygienic and well-ventilated environment in a temperature-controlled room (22+2^{o}C) and humidity (55% +5%), and a 12-hrs light/dark cycle.

Materials & preparation:

Almarai cream cheese was mixed with normal chow and given twice a day to induce hyperlipidemia. Ginger was washed, peeled off, grinded in chopper and measured according to weight of animal and then administered orally with normal diet. Tablet Lipitor (Atorvastatin 10mg) was crushed, and dose was measured according to weight of animal before mixing with normal diet and given orally.

Experimental protocol:

The animals after acclimatization for a period of 1 week were equally distributed into 4 groups, each consisting of 15 animals. During that period animals were fed with normal rodent chow and water. Control group A was continued with normal rodent chow; remaining three groups were fed with High-fat diet (i.e., Almarai Cheese) along with rodent chow for the period of eight weeks. After induction of hyperlipidemia by high-fat diet, experimental group B, labelled as Hyperlipidemic control group[11] was left untreated and fed with normal rodent chow for following eight weeks while experimental groups C and D were treated with oral Ginger 15mg/30gm body weight and Atorvastatin 0.3mg/30gm body weight respectively for eight weeks. All animals were weighed weekly from the start of experiment. Blood samples and liver tissue were obtained from 2, 5 and 8 mice of each group on day 0, 8 and 16 weeks respectively. Blood samples were collected before and after the induction of high-fat diet from retro-orbital sinus.[12] At the end of experiment, blood samples were acquired by direct cardiac puncture after anesthetizing the animals with ether inhalation. Blood samples were collected in plain tubes and centrifuged at 4˚C, 4000 ×g for 10 minutes and processed for the assessment of biochemical parameters (TC, LDL-c, HDL-c, TGs, ALT), after which animals were sacrificed by cervical dislocation.[13] Liver was removed, washed by normal saline to remove blood and dried on filter paper[13] and then preserved in the container filled with 10% formalin for histopathological examination (steatosis, lobular inflammation, ballooning and fibrosis).[14]

Statistical analysis:

Data were analyzed on IBM SPSS version 22. Mean of the quantitative variables in one group was compared with other group by applying independent t test. Mean of the quantitative variables also compared among all four groups by applying one way ANOVA test.

For categorical variables; frequency and percentages (%) were compared among control groups and experimental groups by applying chi square test. P value <0.05 was considered as statistically significant with 95% confidence interval.

Results:

Weight measurement:

Mean of the weight was compared among four groups by applying one way ANOVA and there was no significant difference found between weights of mice. (I.e. p value = 0.06).

Table1: comparison of weight among the hyperlipidemic mice treated with ginger and atorvastatin (n=8) and those not treated with ginger and atorvastatin (n=52)

Weight in grams		N	Mean	±SD	*p* value
Ginger	Yes	8	33.5825	1.672	0.003*
	No	52	36.1119	3.145	
Atorvastatin	Yes	8	34.7500	1.669	0.005*
	No	52	35.9323	3.252	

While comparison of mean of the weight among the mice taking ginger and atorvastatin and not taking ginger and atorvastatin by independent sample t-test showed highly significant difference of weight in both groups. (*p values 0.003 and 0.005 respectively).

Serological assessment:

The mean of lipids were compared among Group A, B, C and D by applying one way ANOVA that showed statistical significant p value of 0.009*****, 0.001*****, <0.001*****, <0.001*****, <0.001***** respectively.as shown in table no 2.

Histopathological assessment

Histological parameters of liver (Steatosis, lobular inflammation, hepatic ballooning and fibrosis) were compared among mice from four groups by applying chi square test which determined significant p value of <0.001*.

Table No 2: Comparison of mean of TGs, LDL, HDL, TC and ALT levels among groups.

Biochemical parameters	Group	SD±	p value
TGs (mg/dl)	A	150.13±46.80	.009*
	B	231.40±36.29	
	C	216.000±113.41	
	D	203.467±36.72	
	Total	200.250±71.80	
LDL (mg/dl)	A	32.667±10.49	.001*
	B	58.067±14.74	
	C	44.133±16.43	
	D	49.400±20.03	
	Total	46.067±17.97	
HDL (mg/dl)	A	127.133±10.15	<0.001*
	B	81.400±21.51	
	C	117.333±37.24	
	D	88.867±17.40	
	Total	103.683±30.07	
TC (mg/dl)	A	157.800±19.98	<0.001*
	B	214.067±29.13	
	C	187.400±38.31	
	D	196.533±33.22	
	Total	188.950±36.45	
ALT (IU/L)	A	24.867±8.19	<0.001*
	B	39.400±4.88	
	C	36.933±10.95	
	D	47.867±19.55	
	Total	37.267±14.48	

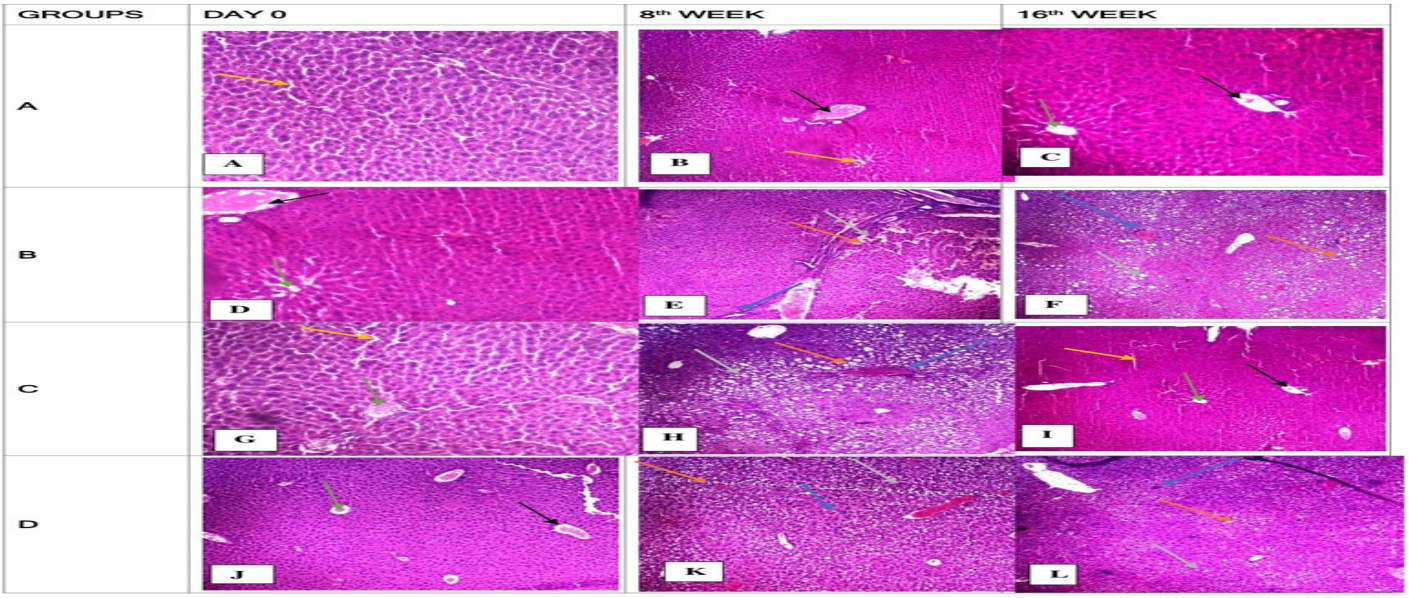

Figure No. 1: Photomicrographs of mice's liver from four groups A, B, C and D at day 0, week 8 and week 16. Photomicrographs A, B and C exhibited normal histomorphology of liver in Normal Control group A as classical hepatic lobule with polygonal hepatocytes radiating like cords from central vein indicated by green arrow, sinusoids between hepatocytes by yellow arrow and portal triad by black arrow throughout experiment. Photomicrographs D, E and F represented hyperlipidemic control group B as normal architecture at day 0 while presence of steatosis designated by grey arrow, hepatic ballooning indicated by orange arrow and lobular inflammation shown by blue arrow after high fat diet at 8th week which were not self-corrected at the end of experiment. Photomicrographs G, H and I showed liver architecture of experimental hyperlipidemic group C treated with ginger depicted as normal histological features at day 0 while significant steatosis, multiple inflammatory foci with hepatic ballooning and fewer perisinusoidal fibrosis at week 8 which were rectified to normal histomorphology by use of ginger at week 16. Photomicrographs J, K and L illustrated similar normal histological features of experimental hyperlipidemic group D treated with atorvastatin at day 0 which were distorted by high fat diet into steatosis, inflammatory foci with hepatic ballooning at week 8 and at the end of experiment these changes were corrected to a lesser degree with some persisted steatosis, hepatic ballooning and inflammation.

Table No 3: Comparison of histological parameters among mice of group A, B, C, and D.

Group	Steatosis				*P* value
	Grade 0	Grade 1	Grade 2	Grade 3	
A	15 (100.0%)	00 (.0%)	00 (.0%)	0 (.0%)	
B	02 (13.3%)	07 (46.7%)	04(26.7%)	02(13.3%)	
C	10(66.7%)	00 (.0%)	03 (20.0%)	02 (13.3%)	<0.001*
D	02 (13.3%)	04(26.7%)	08 (53.3%)	01(6.7%)	
	Lobular inflammation				
	Grade 0	Grade 1	Grade 2		
A	15 (100.0%)	00 (.0%)	00 (.0%)		
B	02 (13.3%)	07 (46.7%)	06 (40.0%)		<0.001*
C	10 (66.7%)	04 (26.7%)	01 (6.7%)		
D	02 (13.3%)	11 (73.3%)	02 (13.3%)		
	Hepatic ballooning				
	Grade 0	Grade 1	Grade 2		
A	15 (100.0%)	00 (.0%)	0 (.0%)		
B	02 (13.3%)	08 (53.3%)	05 (33.3%)		<0.001*
C	10 (66.7%)	00 (.0%)	05 (33.3%)		
D	02 (13.3%)	07(46.7%)	06 (40.0%)		
	Fibrosis				
	Grade 0	Grade 1		Grade 2	Grade 3	
		1a	1b	1c		
A	15(100.0%)	0 (.0%)	0 (.0%)	0 (.0%)	0 (.0%)	0 (.0%)	
B	2 (13.3%)	08 (53.3%)	04(26.7%)	0 (.0%)	0 (.0%)	01(6.7%)	<0.001*
C	10 (66.7%)	01(6.7%)	02(13.3%)	01(6.7%)	01(6.7%)	0 (.0%)	
D	02 (13.3%)	07(46.7%)	04 (26.7%)	0 (.0%)	02 (13.3%)	0 (.0%)	

Discussion:

This animal model-based research study was conducted to observe the effects of hyperlipidemia induced by High fat diet (HFD) on body weight, liver histology and serum lipid levels and their prevention by using ginger and atorvastatin.

The present study has demonstrated that there was significant weight gain in the animals of the experimental groups that were given a high-fat diet (HFD) during the initial 8 weeks of the experiment. Animals in Group C (treated with Ginger) exhibited a noticeable decrease in body weight compared to Groups B and D, as shown in Table 1. Previous studies conducted by MI Talukder and his colleagues on mice fed a butter diet revealed substantial changes in lipid profiles and weight gain with concurrent supplementation of ginger extract.[15] Additionally, Syed Ali Faran et al. concluded that the inclusion of ginger in statin formulations resulted in enhanced antihyperlipidemic, hepatoprotective, and reno-protective effects compared to statins alone.[1] These benefits are attributed to its established lipid-lowering and bile-stimulating properties. Furthermore, it also increases lipase activity, leading to a reduction in fat accumulation in the body and a decrease in body weight.[16] Biochemical parameters measured in this study after the induction of hyperlipidemia showed elevated levels of serum TC, TGs, LDL-c, and ALT, along with a significant decrease in HDL-c levels. In Group C, these levels were reduced to near normal with an increase in HDL-c concentration, whereas in Groups B and D, there was no significant change, with only a slight decrease in TC, TGs, LDL-c, and ALT, and a minor increase in HDL-c, as depicted in Table 2. The results of this study are consistent with those of Paul P et al. and Khosravani M et al., which also revealed that the administration of vanaspati augmented total cholesterol, LDL-C, and triglyceride levels while significantly decreasing HDL-C levels. Simultaneous administration of ginger extract significantly prevented the rise in total cholesterol, LDL-C, and triglyceride levels while elevating HDL.[17,18] Ginger possesses numerous hepatoprotective and antioxidant properties, primarily due to its ability to inhibit de novo cholesterol synthesis by reducing HMG-CoA reductase activity. It also activates cholesterol 7-hydroxylase, leading to the formation of bile acids from cholesterol, which facilitates removal from the body and enhances the transport of circulating LDL-c into the liver, along with increased transport of VLDL-c due to the niacin present in ginger.[19]In this study, as illustrated in Table 3 and Figure 1, histological parameters were assessed after 8 weeks of HFD, revealing that steatosis was graded as 2 (affecting 33%-66% of hepatocytes) in most cases, with a few instances of grade 3 (affecting > 66% of hepatocytes). After the 16th week, steatosis was significantly reversed in Group C mice (treated with ginger), which exhibited grade 0 with a normal structure, in contrast to Group B (untreated) and Group D (treated with atorvastatin), which displayed grade 3 and grade 2 in most of the liver samples, respectively. A research study conducted by Dalila T. Leal et al. in 2019 demonstrated altered liver architecture characterized by fatty vacuolization, peripherally displaced pyknotic nuclei, and balloon cells in animals fed a high-fat diet (HFD), which were nearly restored to normal hepatocytes and sinusoids when treated with various doses of ginger, while non-ginger treated groups showed ballooning and steatosis to a lesser extent.[20] Ginger functions as a hypolipidemic agent primarily by reducing triglyceride levels in the liver, enhancing LDL-c receptors, and inhibiting HMG-CoA reductase, thereby reversing the steatosis induced by HFD.[21] These findings support our current research.

Similarly, when lobular inflammation was examined, most of the animals were found to be in grade 1 (up to 2 inflammatory foci) with few in grade in 2 (2-4 inflammatory foci) after 8 weeks of HFD. Lobular inflammation was absent in Group C having all of animals in grade 0 when compared with Group B and Group D mice showing most of them in grade 1 with few in grade 2 as shown in Table 3. The effects found in this study were same supported by Mehran Rahimlou et al. that ginger essential oil helped in resolution of hepatic lobular inflammation by restricting infiltration of inflammatory cells within parenchyma as ginger reduces TNF- α and cytokines.[22]

As shown in table 3 and figure 1, we observed hepatic ballooning, of grade 2, in all HFD-fed groups with numerous prominent balloon cells. By the end of the experiment, group C mice showed grade 0, while Group B and D displayed mostly grade 1 and a few showed grade 2, respectively. Earlier study conducted in Egypt explained that fatty liver disease induced by intraperitoneal oxytetracycline resulted in fatty degeneration with ballooning of hepatocytes and macro-vacuolization in the cytoplasm which was drastically reversed by ginger,[23] these findings are in agreement with current to study. This property of ginger is also attributed to its ability to decrease the excessive accumulation of lipids by sensitizing insulin receptors which in turn activate lipoprotein lipases causing hydrolysis of triglycerides.[23]

After induction of hyperlipidemia, most of the animals were in grade 1 (c) of fibrosis with few in grade 2 and 3, which were completely resolved in group C animals exhibiting grade 0 and grade 1 (c) in Group B and grade 1 (b) in Group D as displayed in Table 3. Marwa Syed Badawi in a research showed that ginger administration improved piroxicam induced hepatic lobular fibrosis affecting central vein and sinusoids.[24] Fibrosis is characterized by excessive formation and accumulation of extracellular matrix proteins and collagen by hepatic stellate cells as a response to injury. Ginger has effect in treating fibrosis by the presence of its phenolic compounds (gingerols, shogoals) which eradicate elevated free radicals produced by hyperlipidemia. Ginger also stimulates renewal of fibrotic hepatocytes and stabilizes the plasma membrane by limiting the lipid peroxidation.[25]

Conclusion:

This study concluded that ginger, with its rich phytochemical history, is an effective hypolipidemic, antioxidant and hepatoprotective herb with no significant side effects even if used for longer duration in comparison to commercially available drug atorvastatin., when experimented on mice models after feeding with HFD.

Conflict of interest:

Declared nil by all authors

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