



ORIGINAL ARTICLE

Inhibitory Effects of *Solanum lycopersicum* L. on High Fat Diet-Induced Fatty Liver Disease in Rats

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ABSTRACT

The aim of this study was to assess the effects of *Solanum lycopersicum* L. (tomato) extract on fatty liver disease in rats fed with high fat diet. For this end, Male Wistar rats were randomly divided to: 1-Healthy control, 2-Feeding with high fat diet, 3-Feeding with high fat diet plus Clofibrate treatment and 4-Feeding with high fat diet plus tomato extract treatment groups. The rats treated with either high fat diet for induction of hepatic steatosis and high fat diet plus Clofibrate or tomato extract for prevention of liver steatosis, at a period of 6 weeks. At the end of experiment, Serum lipid profile, serum biomarkers of liver tissue injury and hepatic antioxidant activity were statistically compared among the groups using ANOVA and Tukey post-tests. After 6 weeks, high fat diet caused hypertriglyceridemia, hypercholesterolemia and liver dysfunction. Rats fed with high fat diet showed significant increased activities of serum hepatic enzymes, reduction in antioxidants activities, and increased lipid peroxidation index in liver tissue. Treatment with tomato extract significantly reduced increased biomarkers of liver tissue injury and malondialdehyde level, and improved the liver antioxidants and the over accumulation of lipids in serum. Histopathologic findings were parallel with the biochemical findings. The results showed *Solanum lycopersicum* L. extract has protective effects against hepatic steatosis in rats fed with high fat diet.

Key words: Fatty liver disease, *Solanum lycopersicum* L., rat

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INTRODUCTION

Nonalcoholic fatty liver disease is one of the most common causes of chronic liver injury in many countries around the world. It has a broad pathologic spectrum which ranges from simple fatty infiltration of the liver or steatosis, to nonalcoholic steatohepatitis, fibrosis, cirrhosis and to liver failure [1]. Nonalcoholic fatty liver disease is now recognized as the most common type of liver disease and might lead to important public health problems [2].

Triglycerides and cholesterol are of important biological lipids of body that excess get them through the diet is resulted in hypertriglyceridemia [3,4] and hypercholesterolemia [5]. Nonalcoholic fatty liver disease is diagnosed by accumulation of triglycerides in the hepatocytes in consequence of the esterification of free fatty acids and glycerol. Increase in free fatty acids in the liver is driven from three separate sources includes lipolysis (hydrolysis of glycerol and fatty acid from triglycerides) in adipose tissue, high fat diet and de novo lipogenesis [6]. In contrast, fatty acids may used through β -oxidation, de novo esterification to triglycerides and store as fat droplets or excretion in the form of VLDL. Thus, accumulation of fat in the liver can occurs in results of increase the synthesis of fat, reduce in fat excretion or reduce in them oxidation. Donnelly et al., 2005 showed that 60% of liver triglyceride content is driven from influx of fatty acids from adipose tissue, 26% from de novo lipogenesis, and 15% from the diet [7]. Nonalcoholic fatty liver is associated with some histopathologic changes, which is different from steatosis to cirrhosis [8-10]. It was formerly believed that steatosis is a simple phenomenon and has no complications. However, nowadays it is known that fatty liver is vulnerable to factors such as oxidative stress and can lead to Steatohepatitis, which is associated with necrosis, inflammation, fibrosis and cirrhosis [11,12]. In the pathogenesis of nonalcoholic steatohepatitis is assumed that the accumulation of triglycerides in the liver or steatosis will yield to increases the susceptibility of liver to the damages caused by inflammatory

cytokines and lymphokines, mitochondrial dysfunction and oxidative stress [13,14]. Barbuio et al., 2007 showed that oxidative stress is effective in alteration of steatosis to steatohepatitis [15]. However, although liver steatosis may lead to complete hepatic failure, but appropriate and ideal treatment is not established [8]. Biological materials with plant origin forms modern branch pharmacotherapy of disease. Although various pharmacologic agents exist to treat various diseases, but most patients cannot tolerate the side effects of chemical drugs from one hand and plants have very few side effects on patients from other hands. Obviously, it is necessary that several studies must be done on the new drugs in several stages before their entrance to the field of medicine.

Tomato (*Solanum lycopersicum* L.) is one of the most important vegetables worldwide because of its high consumption, year round availability and large content of health related components. The consumption of tomatoes has been proposed to reduce the risk of several chronic diseases such as cardiovascular diseases and certain types of cancer and especially prostate cancer [16,17]. In addition, tomato consumption leads to decreased serum lipid levels and low density lipoprotein oxidation [18]. These health protective effects have been widely attributed to the presence of key antioxidants such lycopene, beta-carotene, vitamin C, quercetin glycosides, naringenin chalcone and chlorogenic acid. All of these are known to contribute significantly to the antioxidant activity of tomato fruit [19]. Among the various protective mechanisms, the antioxidant activity of Tomato is considered responsible for its pharmacological effects. By consideration of antioxidant and hypolipidemic activity of Tomato extract, this matter it will probably be able to protect the liver from steatosis.

To our knowledge, no other biochemical investigations have so far been carried out concerning the effect of Tomato extract on the liver steatosis in high fat diet fed-rats are available in the literature. On the other hand, animal models of liver steatosis and dyslipidemia are valuable for studying the pathogenesis and treatment of steatohepatitis as well as its relationship to metabolic syndrome. Therefore, present study examined the hypothesis that Tomato extract supplementation prevents liver steatosis in a high fat diet model. The results of this study demonstrate that Tomato supplementation prevents liver steatosis and decreases oxidative stress in hepatocytes exposed to high levels of lipid.

MATERIALS AND METHODS

This study carried out during 2012 in the research center of Islamic Azad University. All procedures were conducted under supervision of Animal Rights Monitoring Committee of Islamic Azad University Research Center.

Extract Preparation: Fresh ripe tomato fruits (500g) were washed, seeds removed and the extract homogenized using a blender. The homogenate was then stored in a refrigerator at 4°C until used.

Animals:

Forty male Wistar rats, weighted 180 ± 20 gr and aged 10 weeks old were obtained from the animal breeding center of Islamic Azad University. The rats were divided into 4 equal groups of 10 animals including: 1- normal control, 2- normal rats fed high-fat diets, 3- normal rats fed high-fat diets plus Clofibrate ($320 \text{ mg kg}^{-1}/\text{day}$) and 4- rats which are fed high-fat diets plus Tomato extract (20 ml/kg). Management and husbandry conditions were identical in all groups with 12/12 h light/dark cycle at $21 \pm 2^\circ\text{C}$. Food and water were provided ad libitum.

Experimental design:

In rats were fed with high-fat diets used of high-fat emulsion, which its formula is mentioned in table 1, to induce hepatic steatosis based on Zou et al., 2006 method [20]. All treatment groups received high-fat emulsion at the dose of 10 ml kg^{-1} daily at morning 8 o'clock for 6 weeks. In groups 4 beside of high-fat emulsion, Tomato extract (20 ml/kg) was given through the gavage. Simultaneously, control group received normal saline in same dosage. Group 3 beside of high-fat emulsion received Clofibrate at the dose of $320 \text{ mg kg}^{-1}/\text{day}$ through gavage as suspension in the 2 ml kg^{-1} methylcellulose 0.5% [21]. Control group received 2 ml kg^{-1} methylcellulose 5%.

Table 1: Composition of high-fat emulsion

Constituents	Amount
Corn oil	400 g
Sacarose	150 g
Milk powder	80 g
Cholesterol	100 g
Sodium deoxy colat	10 g
Tween 80	36.4 g
Propilen glikol	31.1 g
Multi vitamin	2.5 g
Salt	10 g
Minerals	1.5 g
Normal saline	300 ml

Measurement of Biochemical factors:

At the end of the experiment, blood samples were collected from the retro-orbital plexus and the sera prepared through centrifuging at 2500 ×g for 15 minutes at 30°C. Serum biomarkers of liver function including ALT, AST [22], ALP [23], albumin, TP [24] and total bilirubin [25] were measured using commercially available kits.

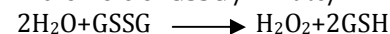
Measurement of Serum lipids:

Serum triglyceride (TG), total cholesterol (TC), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) level were measured enzymatically with commercial assay kits (Nanjing, China). Serum VLDL cholesterol (VLDL-C) was calculated by subtracting LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) from total cholesterol (TC).

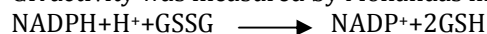
Measurement of antioxidants activities:

All experimental rats were euthanized by cervical dislocation. The rat's Liver were removed immediately and washed in normal saline and homogenate 10% prepared in 1.15% w/v of potassium chloride. The homogenate was centrifuged in 7000 ×g for 10 minutes at 4°C and supernatant were used for measurement of Oxidative stress by determination of malondialdehyde (MDA) as well as antioxidant enzymes (AOE) such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-PX) and glutathione reductase. MDA, SOD, CAT and GSH-PX, GR were measured by using commercially available kits according to the manufacturer's protocol (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Liver homogenate MDA levels were expressed as nmol MDA per mg protein and antioxidant activity was expressed as arbitrary units per mg protein.

Degree of lipid peroxidation in kidney tissue homogenates was determined in terms of thiobarbituric acid reactive substances (TBARSs) formation by following the protocol of Esterbauer and Cheesman [26]. SOD activity was measured by Nishikimi method [27] and was modified by Kakkar method [28]. Each unit of SOD activity was determined as required enzyme concentration for prohibition of creation color at 1 minute, under study conditions. CAT activity was measured by Claiborne method [29] and was based on hydrogen peroxide breakdown. GPX activity was measured by Rotruck method [30] and was expressed as micromole of GSSG /minute/milligram of protein, based on blew reaction:



GR activity was measured by Mohandas method [31], based on blew reaction:

*Microscopic evaluations:*

A small piece of hepatic tissue from the anterior portion of the left lateral lobe was removed for histological analysis. Frozen tissue samples prepared in cryostat. The sample was then sliced into 5 µm sections, and stained with Oil-Red-O for blinded histological assessment [32]. Hepatocytes were assayed from fatty changes aspect like a mentioned method by Wang et al [33] and steatosis were degreed from 0 to 4 (0: without steatosis, 1: <25% steatosis, 2: approximately 26-50% steatosis, 3: approximately 51-75% steatosis, 4: >76% steatosis). The stained 5 µm sections were graded as follows: 0, absent; I, minimal; II, mild; III, modest; IV, severe. The histological changes were evaluated in nonconsecutive, randomly chosen ×200 histological fields using light microscope, NIKON ECLIPSE E200 [34].

Statistical analysis:

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 13.0, was used for statistical analysis. All data are presented as mean ± SEM. Before statistical analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. P<0.05 was considered statistically significant.

RESULTS*Effect of Solanum lycopersicum L. extract on biochemical:*

In group 2, ALT, AST, ALP and TB increased and TP and Alb decreased significantly (p<0.01) in compared with control group. In group 3, high levels of ALT, AST, ALP and TB significantly decreased (p<0.01) to normal levels and levels of TP and Alb increased to their normal boundaries. In group 4, levels of ALT, AST, ALP and TB significantly decreased (p<0.05) and levels of TP and Alb significantly increased (p<0.05) but not reached to normal levels (Table 2).

Table 2: Effect of *Solanum lycopersicum* L. extract on serum biochemical parameters

Groups	Biochemical parameters					
	ALT (U/L)	AST (U/L)	ALP (IU/L)	TB (mg/dl)	Alb (g/dl)	TP (g/dl)
Healthy control	49.51±2.31 ^{bd}	64.72±1.55 ^{bd}	187.72±9.03 ^{bd}	0.83±0.04 ^{bd}	4.42±0.44 ^{bd}	7.95±0.54 ^{bd}
High-fat diet	66.75±3.21 ^{acd}	89.35±2.74 ^{acd}	275.56±11.25 ^{acd}	1.31±0.08 ^{acd}	3.16±0.25 ^{acd}	5.21±0.21 ^{acd}
High-fat diet+ Clofibrate	50.69±2.15 ^b	64.20±1.27 ^b	199.87±7.63 ^b	0.89±0.06 ^b	4.35±0.38 ^b	7.05±0.44 ^b
High-fat diet+ Extract	60.13±3.10 ^{ab}	77.36±2.86 ^{ab}	231.93±8.42 ^{ab}	1.09±0.06 ^{ab}	3.64±0.25 ^{ab}	5.91±0.31 ^{ab}

Values are presented as mean ± SEM for 10 rats in each group.

a, significant difference with group 1; b, significant difference with group 2; c, significant difference with group 3; d, significant difference with group 4 (p<0.05).

Histopathological findings:

In microscopic studies no abnormalities was found in the livers of control group rats. But in group 2 rats' which fed with high-fat diet for 6 weeks, sever steatosis was found as micro and macrovesicular fatty changes accompanied hepatitis. Clofibrate prevented from steatosis in group 3 rats. In groups 4, Tomato extract prevented from fatty changes in hepatocytes obviously. Effect of Tomato extract on the pathologic grading of hepatic steatosis in rats fed high-fat diet is listed in Table 3.

Table 3: Effect of *Solanum lycopersicum* L. extract on the hepatic steatosis

Groups	Hepatic steatosis score					P
	0	1	2	3	4	
Healthy control	10	0	0	0	0	
High-fat diet	0	0	1	2	7	a
High-fat diet+ Clofibrate	7	2	1	0	0	c
High-fat diet+ Extract	5	3	1	1	0	bd

Each group contains 10 rats. a: p<0.01; b: p<0.05 in compared with control group. c: p<0.01; d, p<0.05 in compared with high-fat fed diet group.

Effect of *Solanum lycopersicum* L. extract on metabolism of fat

Clofibrate in groups 3 significantly (p<0.001) decreased, markedly increased serum levels of TG, total cholesterol, LDL and VLDL compared with group 2 and significantly (p<0.01) increased slightly decreased serum levels of HDL than group 2. In group 4, Tomato extract significantly (p<0.01) decreased serum levels of total cholesterol, LDL and VLDL compared with group 2 and significantly (p<0.05) increased serum levels of HDL than group 2. (Table 4).

Table 4: Effect of *Solanum lycopersicum* L. extract on lipid levels

Groups	TG (mg/l)	Total cholesterol (mg/l)	LDL (mg/l)	VLDL (mg/l)	HDL (mg/l)
Healthy control	88.68±4.21	83.65±3.58	13.69±0.83	19.45±1.16	50.51±3.26
High-fat diet	233.61±6.90	218.14±7.81	122.72±4.75	49.52±2.21	45.90±2.34
High-fat diet+ Clofibrate	95.87±3.42 ^c	110.28±4.29 ^c	25.54±1.09 ^c	31.32±1.15 ^c	53.42±4.38 ^b
High-fat diet+ Extract	182.52±4.61 ^b	139.35±5.16 ^b	52.65±2.88 ^b	35.16±2.34 ^b	51.54±3.95 ^a

Values are presented as mean ± SEM for 10 rats in each group.

a: p<0.05; b: p<0.01; c: p<0.001 in compared with high-fat fed diet group.

Effect of *Solanum lycopersicum* L. extract on antioxidants activities of liver

In group 2, Hepatic levels of antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase compared with group 1 (normal control), significantly (p<0.01) reduced and the levels of malondialdehyde significantly (p<0.01) increased. Clofibrate in groups 3 significantly (p<0.01) increased, markedly decreased levels of SOD, CAT, GPX and GR compared with group 2 and significantly (p<0.01) decreased slightly increased levels of malondialdehyde than group 2. In group 4, Tomato extract significantly (p<0.05) decreased levels of ALT, AST, ALP and TB compared with group 2 and significantly (p<0.05) increased levels of TP and Alb but not reached to normal levels. Data are showed in table 5.

Table 5: Effect of *Solanum lycopersicum* L. extract on anti-oxidative activity

Groups	Biochemical parameters				
	MDA nmol/g protein	SOD U/mg protein	CAT U/mg protein	GPX U/mg protein	GR U/mg protein
control	3.54±0.16 ^{bd}	13.64±0.54 ^{bd}	64.66±2.13 ^{bd}	22.84±1.65 ^{bd}	123.37±5.65 ^{bd}
high-fat diet	5.18±0.21 ^{acd}	9.13±0.32 ^{acd}	41.74±1.15 ^{acd}	17.49±0.83 ^{acd}	88.85±3.52 ^{acd}
high-fat diet+ Clofibrate	3.59±0.18 ^b	12.53±0.52 ^b	60.84±1.74 ^b	21.95±1.54 ^b	116.13±3.42 ^b
high-fat diet+ Extract	4.78±0.24 ^{ab}	10.62±0.81 ^{ab}	54.14±1.35 ^{ab}	19.73±1.28 ^{ab}	108.79±4.11 ^{ab}

Values are presented as mean ± SEM for 10 rats in each group.

a, significant difference with group 1; b, significant difference with group 2; c, significant difference with group 3; d, significant difference with group 4 ($p < 0.05$).

DISCUSSION

The increased activities of biomarker enzymes, AST, ALT and ALP are suggestive of liver injury [35]. Because these serum liver biomarkers disorders have been documented in hepatic steatosis [33,36], their levels were studied. Increased plasma activities of AST, ALT and ALP were found in high fat diet fed rats, indicating damage to liver cells. These results were consistent with the findings reported by Chidambaram and Venkatraman [35]. Treatment with Tomato extract notably prevented the elevation of these enzymes to an extent that was comparable to the Clofibrate.

The biochemical findings were matched with histopathological verification. Rats fed with high-fat emulsion for 6 weeks developed a higher degree of steatosis. However, histopathological assessment of liver tissues from high fat emulsion induced rat hepatic steatosis, displayed the antihepatosteatosis effects of Tomato extract. Administration of Tomato extract resulted in prevention of hepatic fatty deposition in hepatocytes. Histopathological changes in agreement with biochemical findings were concordant with those of previously reported [33].

Our results show that high fat diet caused significant decreases in SOD, CAT, GPx and GR activities. The derangement in enzymatic antioxidant potential indicates that high fat diet fed rats is unable to cope up with excess free-radical formation which leads to tissue damage. A body of evidence indicates that accumulation of fat in the liver increases the susceptibility to other insults such as oxidative stress that results in the progression of steatosis to steatohepatitis, fibrosis and cirrhosis [37].

Considering the recently recognized association between oxidative stress and inflammation [35], the present experiment confirms that high fat diet could result in oxidative liver injury. Induction of oxidative stress is evident from the increased peroxidation marker (MDA) and inadequate antioxidant enzymes status in liver of rats fed high fat diet. We estimated antioxidant activities of Tomato extract by determination of hepatic MDA content and antioxidant enzymes activity. High fat diet fed caused an increase in liver MDA content but a decrease in liver antioxidant enzymes activity compared with normal control group. Tomato extract significantly improved the antioxidant defense mechanisms in high fat diet fed rats.

These results suggest that the imbalance between oxidative stress generation and antioxidants formation could occur after high fat diet fed, and Tomato extract could prevent this pathological process, indicating its therapeutic and preventive effect on hepatosteatosis induced by high fat ingestion. Antioxidant activity of Tomato extract is concordant with those of other investigators [38,39]. The results of biochemical tests together with histological observations suggest that Tomato extract treatment lowers steatosis and prevents peroxidative damage and the effects are comparable with that of Clofibrate.

To analyze the possible role of Tomato extract in lipid metabolism which is the key factor in fatty liver formation, serum TG, TC, VLDL-C, HDL-C and LDL-C were investigated. After 6 weeks of treatment, the serum levels of TG, TC, VLDL-C, and LDL-C was markedly increased in the high fat diet fed group compared to those in the control group. This finding was parallel to the previous study [20]. Treatment of high fat diet fed rats with Tomato extract caused considerable restoration of lipid levels to that of control. The increased serum levels of TG, TC, VLDL-C and LDL-C were significantly suppressed, whereas the decreased serum HDL-C level was obviously elevated by Tomato extract treatment in high fat diet fed rat. Results of the histological changes in high fat diet rats, widespread deposition of lipid droplets inside the parenchymal cells, are consistent with the result of the biochemical analysis. This result suggests that Tomato extract can prevent hepatosteatosis via down regulation of accumulation of lipid in serum and liver. Liver plays a key role in lipid metabolism. Hepatic steatosis refers to the excessive accumulation of lipids within hepatocytes due to imbalance between lipid formation and lipid degradation [40].

Hypercholesterolaemia, hypertriglyceridaemia, low level of HDL-C and high level of LDL-C are the most common impairments in lipid homeostasis in patients with steatosis [8]. Previous study has showed Tomato has hypolipidemic effects [18]. In this study, Tomato extract significantly improved both the biochemical and histological evidence of hepatic lipid accumulation. These results indicate that Tomato extract attenuates the disorder of lipid metabolism in liver resulted from high fat diet fed.

This study reveals that Tomato extract prevents high fat fed induced accumulation of lipid in rat liver. The preventive effect of Tomato extract is mediated through down-regulation the levels of TG, TC, VLDL-C and LDL-C and elevation HDL-C synthesis. These changes are associated with decreasing in serum biomarkers of hepatic injury as well as attenuation of oxidative stress formation by Tomato extract treatment. These results demonstrate that Tomato extract has preventive effects against high fat diet induced rat fatty liver. It is noteworthy that this experiment has been performed on animal, so further studies are needed to examine whether similar findings would be obtained in humans.

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