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Influence of dietary supplementation of Garden cress (*Lepidium sativum* L.) on liver histopathology and serum biochemistry in rats fed high cholesterol diet

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ABSTRACT

The objective of current study was to evaluate the effects of *Lepidium sativum* (LS) on liver histopathology and serum biochemistry in rats fed with high cholesterol diet. A total of 32 rats were divided into four equal groups. The rats of first group (control group) were fed with basal diet, whereas the rats of second group were fed with basal diet mixed with cholesterol (1%). The rats of third and fourth groups were fed with high cholesterol (1%) diet mixed with *Lepidium sativum* powder at 3 g and 6 g/kg diet, respectively. Total cholesterol, triacylglycerol and alanine transaminase (ALT) activity were increased significantly in the rats fed with high cholesterol diet as compared to control group. LS reduced total cholesterol and ALT; however, higher dose (6 g/kg diet) was found better than lower dose (3 g/kg diet) in reducing serum triacylglycerol. Histopathological findings revealed that liver of cholesterol-treated rats showed varying degrees of vacuolar degeneration, fatty changes, fatty cysts, and lobular disarray. Livers of the LS-treated rats revealed mild to moderate degree of recovery. Conclusively, high dose of LS is recommended as hypocholesterolemic and hypolipidemic agent in rats.

Keywords

Biochemistry, Histology, *Lepidium sativum*, Liver tissues, Serum

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INTRODUCTION

Medicinal plants have gained great attentions to be used as food additives for animals and as spices for human (Elmahdi et al., 2014). *Lepidium sativum* L. (LS; garden cress) is related to Brassicaceae (cabbage family) and called as *Hab el Rashaad* or *Thufa* in Saudi Arabia particularly in Hijaz, Al-Qaseem and the Eastern Province (Bafeel and Ali 2009). The seeds of LS are used in different medicinal applications, and the leaves of LS are used in salad (Maier et al., 1998). The LS was used as antidiabetic (Eddouks and Maghrani 2008), anti-asthmatic, diuretic (Chopra et al., 1986; Eddouks et al., 2002), hypotensive (Maghrani et al., 2005), anticarcinogenic (Zhang and Talalay 1994; Kassie et al., 2003a), and antibacterial (Aburjai et al., 2001) agent. The most effective ingredient present in LS is isothiocyanates, which is formed with glucosinolates (Kassie et al., 2002). The hepato-protective role of LS against hepatotoxicants (Kassie et al., 2002, 2003b) and fatty liver (Abuelgasim et al 2008) were also reported. Hyperlipidemia is the most predisposing factor of atherosclerosis and chronic heart disease (Wang et al., 1997).

Focal accumulation of cholesterol in intima of large and medium-sized arteries may form atheromas (Varshney and Sharma, 1996) resulting narrowing the arterial lumen, damage the underlying media and frequently become ulcerated and calcified, and subsequently reduces blood flow to the myocardium (Goldstein and Brown, 1990). Success in lowering serum cholesterol could reduce coronary artery disease. Several chemical

drugs are used in lowering cholesterol; however, high price and side effects are the main disadvantages (Thomas, 2003). To overcome these problems, currently attentions are directed to the traditional medicine. LS plant and its seeds are known as one of the most popular medicinal plants in Saudi Arabia. However, reports on effects of this herb as hypolipidemic and liver and kidney functions improving factor are very few. Therefore, the present study was aimed to investigate the potential use of LS as hypolipidemic and hypocholesterolemic agent considering serum biochemical and histological pictures of rats fed with high cholesterol diet.

MATERIALS AND METHODS

Chemicals and kits: Diagnostic kits for serum total proteins, albumin, total lipid, triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c), alanine aminotransferase (ALT) and aspartate amino transferase (AST), alkaline phosphatase (ALP), urea, uric acid and creatinine were purchased from ELIPSE, United diagnostic industry, UDI, Dammam, Saudi Arabia. Pure cholesterol (Cat# C3045) was purchased from Sigma-Aldrich, USA. Routine chemicals and solvents used in the study were of highest grade and commercially available.

Plant material: The plant used in this study was purchased from local market in Al-Ahsa, Saudi Arabia. The plant was identified and authenticated as *Lepidium sativum* L. by Botanists in College of Agricultural Sciences. LS seeds were ground as fine powder, and the powder was stored in air tight container.

Animals and treatment: A total of 32 albino rats (200-250 g) were obtained from Laboratory House of College of Veterinary Medicine and Animal Resources, King Faisal University, Al-Ahsa, Saudi Arabia. The rats were acclimated for 10 days before starting experiment. All animals were housed in standard cages (8 rats/cage), fed with standard laboratory diet and tap water *ad libitum*. The experimental animals were housed in air-conditioned rooms at 21-23°C and 60-65% of relative humidity, and kept on a 12 h light/12 h dark cycle. The animals received humane care in accordance with the Guide for the Care and Use of Laboratory Animals, published by ethics of scientific research committee of King Faisal University, Saudi Arabia (#DSR 140107).

Induction of hypercholesterolemia: One gram of pure cholesterol powder was added to each 99 g of basal diet except the control for induction of hypercholesterolemia according to Sharma (1984) and Pandya et al. (2006).

Experimental groups and protocol: Rats were fed on standard diet, and were divided randomly into 4 groups comprising 8 rats in each group.
Group 1: Rats fed on basal diet without any additives and served as a control group.
Group 2: Rats fed on 1% cholesterol diet.
Group 3: Rats fed on 1% cholesterol diet mixed with LS seeds powder (at 3 g/kg cholesterol diet, as described by Chauhan et al., 2012).
Group 4: Rats fed on 1% cholesterol diet, and treated with LS seeds powder (at 6 g/kg cholesterol diet; double of the first dose).

Samples collection: Blood samples were collected after two weeks following treatment to confirm the induction of hypercholesterolemia. At the end of the experiment, the overnight fasted animals (the control and experimental animals) were sacrificed under light ether anesthesia. Blood samples were collected by cardiac puncture and 5 mL of blood samples were collected in plain vacutainers. Sera were prepared and stored at –20°C until biochemical analysis. Liver tissues were cut in small pieces and immersed in neutral buffered formalin for histopathological analysis.

Biochemical analysis: Commercial diagnostic kits (United Diagnostic Industry, UDI, Dammam, Saudi Arabia) were used for the determination of total proteins (EP56-660), albumin (EP03-570), Glucose (EP37L-660), ALT (EP07-500), AST (EP15-500), creatine kinase, CK (EP28-310), blood urea nitrogen (BUN; EP20-420), Uric acid (EP61-620), creatinine (EP33K-660), TAG (EP59-660), cholesterol (EP24-660), HDL-c (EP41HD), Calcium (EP22-660), Phosphorus (EP46-660) Magnesium (EP50-660) and Chloride (EP27-500) on ELIPSE full automated chemistry analyzer (Rome, Italy). Concentration of the biochemical constituents was calculated according to the instructions of the manufacture. Very low density lipoprotein cholesterol (VLDL-c) was calculated by division of TAG by 5, while LDL-c was calculated by subtracting the values of sum HDL-c and VLDL-c from total cholesterol value, as described by Bauer (1982).

Histopathological examination: Liver tissues were cut in small pieces and immersed in neutral buffered

formalin for 24 h. The fixed tissues were processed routinely, embedded in paraffin, sectioned, deparaffinized and rehydrated, as described by Bancroft and Gamble (2002). The effect of high cholesterol diet and LS on liver tissues was evaluated by assessing the morphological changes in the liver sections stained with hematoxylin and eosin (H&E), using standard techniques.

Statistical analysis: All data was presented as mean±standard error of mean by using one way analysis of variance ANOVA. All tests were performed using computer package of the statistical analysis system (SAS, 2002).

RESULTS AND DISCUSSION

It has been postulated that, decrease in serum cholesterol by 1%, reduced the risk of chronic heart disease by 2% (Jain et al., 2007). The synthetic hypolipidemic drugs are expensive beside having side effect as liver and muscle toxicity, renal insufficiency and hyperthyroidism (Moosa et al., 2006). LS was frequently used as antidiabetic (Eddouks and Maghrani 2008), anti-asthmatic, diuretic (Chopra et al., 1986; Eddouks et al., 2002), hypotensive (Maghrani et al., 2005), hepato-protective (Kassie et al., 2002, 2003b) hypolipidemic (Abuelgasim et al 2008), anticancer (Fekadu et al., 2003) and antibacterial (Aburjai et al., 2001) agent. However, the hypolipidemic and hypocholesterolemic effect of this medicinal plant has not been completely elucidated. In the current study, the effect of Garden cress *(Lepidium sativum* L.) was investigated on histopathological picture of liver tissues and serum biochemical parameters of rats fed with high cholesterol diet.

The effect of two doses of LS (3 g and 6 g/kg diet) on glucose, total proteins and lipid profiles of rats fed high cholesterol diet are presented in **Table 1**. These findings indicated that, total cholesterol was increased in rat fed high cholesterol diet (33.4±0.2 mg/dL) as compared to control groups (28.1±0.1). However, inclusion of LS in high cholesterol diets (3 g and 6 g/kg diet) reduced serum total cholesterol (32.1±0.1; 29.3±0.1), respectively as compared to rats fed high cholesterol diet (33.4±0.2), and toward the normal control values (28.1 ± 0.1). These findings indicated that triacylglycerol was increased in rat fed high cholesterol diet (43.6±0.4 mg/dL) as compared to control groups (40.9±1.6). However, high dose of LS (6 g/kg diet) only reduced triacylglycerol (30.0±1.0) as compare to rats fed high cholesterol diet (43.6±0.4) and rats fed LS (3 g/kg diet; 44.2±3.2) toward the normal control values (40.9±1.6). The values of total proteins, albumin, glucose, HDL-c, LDL-c and VLDL-c remained comparable to those of control groups. The insignificant differences in serum total proteins, albumin, globulins and glucose of all experimental groups observed in the current study come in accordance with previous report of Al-Taee (2013) who described that total protein was not changed significantly in rabbits kept on phenol and terpen extracts of LS. However, the findings of our study disagreed with Chauhan et al. (2012) and Korish and Arafah (2013) who demonstrated that rats fed high fat and cholesterol diet exhibited significant increase in serum glucose concentration whereas LS seed powder caused to reduce toward the control values (Chauhan et al., 2012).

In the current study, significant increase of total cholesterol and triglycerides in rats fed high cholesterol diet was observed as compared to control group. These findings are in agreement with several other works (Das et al., 1997; Al Hamedan, 2010; Chauhan et al., 2012; Korish and Arafah, 2013). This hyperlipidemia could be related to enhanced de-esterification of abundant free fatty acids and decreased lipoproteins (Jensen 2008). In contrast to the present study, few previous reports demonstrated significant increase in serum LDL-c and VLDL-c in rats fed high fat and cholesterol with significant decreases in HDL-c (Al Hamedan, 2010; Chauhan et al., 2012; Korish and Arafah, 2013). The hypolipidemic and hypocholesterolemic effects of LS observed in the present study come in accordance with previous reports of Al Hamedan (2010 and Chauhan et al. (2012) in rats fed high cholesterol diet. These authors also reported that LS seed powder caused significant reduction of LDL-c and VLDL-c with significant increase in HDL-c in serum of rats fed high fat and cholesterol diet as compared to the control values; which disagree with the findings of the present study. The hypolipidemic effect of *Lepidium sativium* might be attributed to inhibition of absorption and enhanced excretion of lipids (Chauhan et al., 2012). The hypocholesterolemic effect of *Lepidium sativium* might be attributed to inhibition of cholesterol biosynthesis. This is through the inhibition of HMG-CoA reductase, the rate-limiting enzyme that mediates the first step in cholesterol biosynthesis. Biochemical changes and alterations in enzymes activities induced a stress on liver function. The present findings summarized in **Table 2** indicated that, ALT activity was increased in rat fed high cholesterol diet (26.5±0.6 IU/l) as

Table 1. Glucose, protein and lipid profiles of rats fed high cholesterol diet and treated with two doses of *Lepidium sativum* (3 g and 6 g/kg diet).

Parameters	Groups			
	1	**2**	**3**	**4**
Glucose (mg/dL)	100.2 ± 2.0	105 ± 4.0	107.3 ± 4.0	105.7 ± 5.0
Total proteins (g/dL)	4.7 ± 0.5	4.5 ± 0.4	4.0 ± 0.5	4.0 ± 0.5
Albumin (g/dL)	3.4 ± 0.3	3.5 ± 0.5	3.4 ± 0.2	3.6 ± 0.2
Globulins (g/dL)	1.3 ± 0.1	1.0 ± 0.2	1.2 ± 0.1	1.2 ± 0.2
Triglycerides (mg/dL)	40.9 ± 1.6	43.6 ± 0.4*	44.2 ± 3.2	30.0 ± 1.0**
Total cholesterol (mg/dL)	28.1 ± 0.1	33.4 ± 0.2*	32.1 ± 0.1**	29.3 ± 0.1**
HDL-c (mg/dL)	13.9 ± 1.5	12.9 ± 1.6	13.0 ± 1.0	13.5 ± 1.4
LDL-c (mg/dL)	8.5 ± 1.3	11.2 ± 1.5	12.7 ± 1.2	14.0± 3.0
VLDL-c (mg/dL)	8.2 ± 1.2	8.3 ± 1.1	8.5 ± 1.1	8.0 ± 1.0

Each value represents the mean ± standard deviation of 8 rats.
HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; VLDL-c: Very low density lipoprotein cholesterol
*Mean values are significantly (p<0.05) different compare to the control (group 1). **Mean values are significantly (p<0.05) different compare to cholesterol treated rats (group 2).
Group 1: Rats fed basal diet and served as control group
Group 2: Rats fed basal diet mixed with cholesterol powder 1%
Group 3: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (3 g/kg diet)
Group 4: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (6 g/kg diet)

Table 2. Liver function Biomarkers of rats fed high cholesterol diet and with two doses of *Lepidium sativum* (3 g and 6 g/kg diet).

Parameters	Groups			
	1	**2**	**3**	**4**
ALT (IU/L)	23.7 ± 0.4	26.5 ± 0.6*	20.8 ± 0.5**	23.5 ± 0.7**
AST (IU/L)	71.4 ± 5.1	64.4 ± 4.9	68.5 ± 4.0	66.9 ± 5.0
CK (IU/L)	510.4 ± 10.1	493 ± 11.2	511.1 ± 10.1	512.6 ± 10.1

Each value represents the mean ± standard deviation of 8 rats.
ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; ACP: Acid phosphatase; CK: Creatine kinase
*Mean values are significantly (p<0.05) different compare to the control (Group 1). **Mean values are significantly (p<0.05) different compare to cholesterol treated rats (Group 2).
Group 1: Rats fed basal diet and served as control group
Group 2: Rats fed basal diet mixed with cholesterol powder 1%
Group 3: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (3 g/kg diet)
Group 4: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (6 g/kg diet)

Table 3. Kidney markers of rats fed high cholesterol diet and treated with two doses of *Lepidium sativum* (3 g and 6 g/kg diet).

Parameters	Groups			
	1	**2**	**3**	**4**
BUN (mg/dL)	8.0 ± 1.3	7.0 ± 1.2	8.0 ± 1.2	8.2 ± 1.1
Creatinine (mg/dL)	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
Uric acid (mg/dL)	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1

Each value represents the mean ± standard deviation of 8 rats.
BUN: Blood urea nitrogen
Group 1: Rats fed basal diet and served as control group
Group 2: Rats fed basal diet mixed with cholesterol powder 1%
Group 3: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (3 g/kg diet)
Group 4: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (6 g/kg diet)

Table 4. Electrolytes profile of rats fed high cholesterol diet and treated with two doses of *Lepidium sativum* (3 g and 6 g/kg diet).

Parameters	Groups			
	1	**2**	**3**	**4**
Calcium (mg/dL)	5.1 ± 0.5	5.5 ± 0.4	5.2 ± 0.4	5.0 ± 0.4
Phosphorus (mg/dL)	2.3 ± 0.5	2.8 ± 0.5	3.4 ± 0.5	3.8 ± 0.5
Magnesium (mg/dL)	4.0 ± 0.3	4.4 ± 0.2	4.8 ± 0.2	4.9 ± 0.3
Chloride (mEq/L)	44.4 ± 5.0	53.9 ± 6.0	59.0 ± 4.0	60.1 ± 3.0

Each value represents the mean ± standard deviation of 8 rats.
Group 1: Rats fed basal diet and served as control group
Group 2: Rats fed basal diet mixed with cholesterol powder 1%
Group 3: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (3 g/kg diet)
Group 4: Rats fed basal diet mixed with cholesterol powder 1% and *Lepidium sativum* powder (6 g/kg diet)

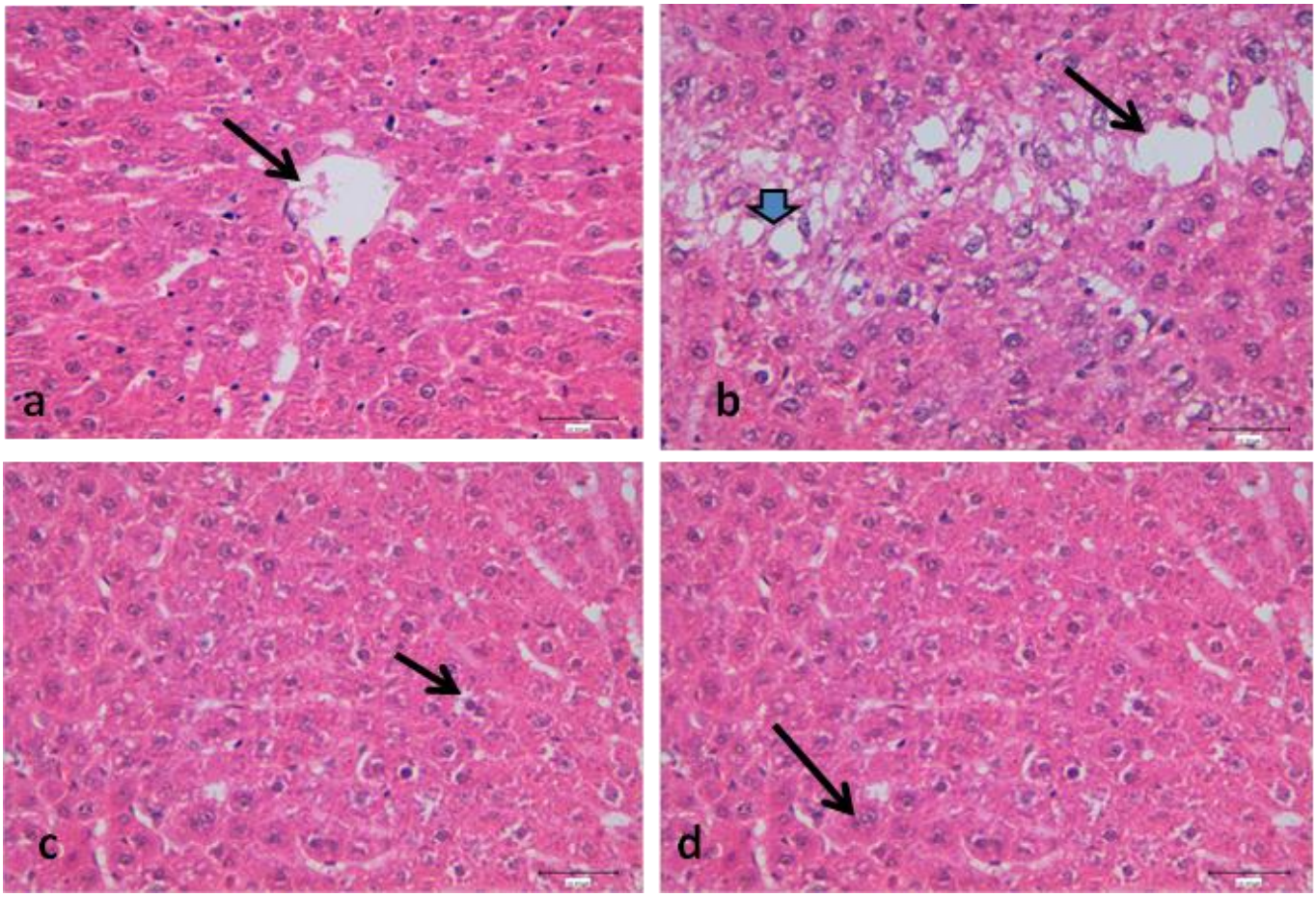

Figure 1. Histopathological image of rat liver fed high cholesterol diet and treated with two doses of *Lipidium sativum* (3 and 6 g/kg diet). (1a) Liver of control rats showing normal central vein and regular hepatic cords (arrow), HE bar = 40 µm. **(1b)** Liver of cholesterol treated rats showing fatty degeneration (arrowhead) and fatty cysts (arrow), HE bar = 40 µm. **(1c)** Liver of Lepidium sativum (LS) powder 3 g/kg diet treated rats showing mild vacuolar degeneration of hepatocytes (arrow), HE bar = 40 µm. **(1d)** Liver of *Lepidium sativum* (LS) powder 6 g/kg diet treated rats showing the same for 1c, mild vacuolar degeneration of hepatocytes (arrow), HE bar = 40 µm.

compared to control groups (23.7±0.4). However, inclusion of LS (3 g and 6 g/kg diet) in high cholesterol diets reduced serum ALT activity (20.8±0.5; 23.5±0.7), respectively as compared to rats fed high cholesterol diet (26.5±0.6) and control values (23.7±0.4). The activities of AST and CK remained comparable to that of control groups. The increase in ALT activity of rats fed high cholesterol diet comparing to control as

observed in the current study agreed with previous reports in rats fed high fat and cholesterol diet (Al Hamedan, 2010; Chauhan et al., 2012). The supplementation of LS in diet caused a reduction in activity of these enzymes as compared to cholesterol fed rats. Based on this result, our findings could argue that LS may have hepatoprotective effect (Al Hamedan, 2010). The data described in **Table 3** indicated that, kidney functions were not disturbed in all experimental groups as reflected on the estimated values of BUN, uric acid, creatinine. Electrolyte concentration (calcium, phosphorus, magnesium and chloride) was not changed in all experimental groups as compared to control (**Table 4**). Kidney function was not affected in rats of all experimental groups, as reflected on the unchanged values of BUN, creatinine and uric acid. However, previous report (Al Hamedan, 2010) demonstrated that LS seed reduced the levels of urea and creatinine, which was increased as a result of inclusion of high cholesterol level (2%) for three weeks in the diet of rats. Electrolytes concentrations (calcium, phosphorus, magnesium and Chloride) were not changed in all experimental groups as compared to the control (**Table 4**).

Light microscopic examination of liver tissue in the control group stained by H&E showed central veins surrounded by polygonal cells arranged in regular cords separated from each other by sinusoids (**Figure 1a**). Liver of the cholesterol treated rat showed varying degrees of vacuolar degeneration and differences in size, shape, and staining affinity. The majority of vacuolar degeneration was fatty degeneration which extended to outward appearance of fatty cysts (**Figure 1b**). The resulting irregularity of liver cell plates is termed lobular disarray. LS (3 g/kg diet; **Figure 1c**) and LS (6 g/kg diet; **Figure 1d**) treatments were more or less similar to each other, in which the main hepatocytes revealed mild to moderate degree of recovery. Both the doses attenuated the hepatic fat accumulation and improved the architecture of hepatocytes. The current histopathological findings (**Figure 1**) regarding the effect of high cholesterol diet on liver tissues come in accordance with previous work in human (Korish and Arafah 2013).

The current study demonstrated the histopathological report for the first time regarding the protective effects of LS on hepatic fatty changes induced by administration of high cholesterol diet in rats. In previous work of Bafeel and Ali (2009), it was reported that, oral water suspension of LS seed powder (2, 4, 8 g/100/mL) showed hepatotoxicity to rats, showing an increase in serum total protein, albumin and ALT; however, AST, GGT were remained within normal levels. However, the authors did not use sophisticated techniques for verification of their arguments such as enzyme immunoassay and electron microscopic study of hepatic tissue. And, they claimed that the effects of LS on liver structure and function observed in their study were preliminary work and further investigation was needed to clarify the cytological and biological effects of feeding on individual LS constituents for more prolonged periods. In addition, recent results showed that acute and subchronic feeding of LS seed for 14 weeks did not produce any toxic effects in male and female rats and thus can be considered non-toxic and safe (Datta et al., 2011).

CONCLUSION

Higher dose of *Lepidium sativum* (6 g/kg diet) is safe to liver and kidney function in rats and acts as effective hypolipidemic hypocholesterolemic agent, whereas low dose (3 g/kg diet) of the same plant is efficient only as hypocholesterolemic agent in rats fed high cholesterol diet. Further molecular studies are needed to clarify the exact mechanism of action of *Lepidium sativum* as antihyperlipiemic and antihypercholesterolemic agent. This might open new perspectives of animal and human health sciences.

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