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Artichoke Leaves Water Extract Attenuate Oxidative Stress and Regulates Lipid Profile in Rats Fed High Fat Diet

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ABSTRACT

High fat diet induces excessive body fat storing by increasing mass of adipose tissue which leads to lipid profile abnormalities. Artichoke is a plant that traditionally used for treatment of various diseases. This research aimed to study the role of supplementing low or high doses of water extract of artichoke leaves in rats fed HFD. In this regard, four rat groups were established as follows: control group, high fat diet group, Low dose artichoke+ HFD group (600 mg /kg b.w/day) after three weeks following obesity induction, and high dose artichoke +HFD group (1500 mg /kg b.w /day). Body weight gain, serum lipid parameters, liver enzymes, antioxidant status, lipoprotein lipase gene expression and histology of adipose tissue and liver were examined. Results showed that HFD increased body weight, lipid parameters and causes abnormal liver enzyme levels along with disturbance of antioxidant status, fat droplets accumulation and enlargement of adipose tissues. These parameters were counteracted by supplementing either low or high dose of artichoke extract, showing the mitigating effect of artichoke against HFD side effects. It was revealed that the hypolipodemic and hepatoprotective effects were more observable in low dose of extract than that of high dose.

Key words: *Cardiovascular Diseases, Osteoprotegerin, Obesity, Lipid Profile.*

INTRODUCTION

Medicinal plants contain phenolic compounds and flavonoids that provide defense against reactive oxygen species (ROS) and diseases related to oxidative stress such as atherosclerosis and inflammation. Recently, lots of studies discovered the use of herbal plants to be alternative and scientifically protected medicine [1].

Artichoke (*Cynarascolymus*L.) is a plant extensively cultivated in Mediterranean countries and contain bioactive compounds, such as caffeoylquinic acid derivatives and flavonoids. The artichoke leaf extract has been used for hepatoprotective, antimicrobial and cholesterol lowering functions. Most studies demonstrated that artichoke extract is efficient antioxidant and its health-protective prospective was accredited to its antioxidant power [2].

Artichoke leaf extracts were used alone or in combination with other herbs in preparing herbal teas and medicinal products. Polyphenolic components were mostly found in artichoke leaves more than heads, their active compounds protect against lipid peroxidation, protein oxidation and boost the activity of glutathione peroxidase [3].

Obesity is a result of high-fat diet (HFD), leading to multi-factorial diseases, and results in diabetes, hypertension and coronary heart diseases [4], In addition, obesity has dangerous effects on liver and antioxidant

enzymes. Different studies have recommended that the increase in intracellular reactive oxygen species, is related to high fat diet [5].

The study aimed to explore the role of supplementing low or high doses of water extract of artichoke leaves in rats fed HFD on liver function and oxidative stress.

MATERIALS AND METHODS

Plant extract:

For this experiment, artichoke leaf extract was obtained from Now Foods company, USA. The extract was dissolved in water, and prepared as high dose and low dose for rat treatments.

Preparation of high fat diet (HFD)

High fat diet (containing 45 % vegetable margarine) was prepared by mixing standard pellets with vegetable margarine.

Experimental animals and diet

Forty male Albino rats were housed at King Fahd Medical Research Center Animal Facility Breeding Colony and kept at constant temperature (25 °C) under controlled conditions of light/dark cycle. During acclimatization period, rats were free accessed to water and regular laboratory diet. The study was verified by the Ethical Committee of King Fahd Medical Research Center, Jeddah, KSA.

Preparation of high fat diet (HFD)

High-fat diet (containing 45 % vegetable margarine) was prepared by mixing with standard pellets with vegetable margarine.

Animal groups and Treatments:

Animals were grouped into four groups (ten / each) as following:

(1) Healthy control group
(2) High fat Diet obese rats: (HFD) obesity was induced by feeding rats on high fat diet for 8 weeks and continue feeding HFD for further 3 weeks.
(3) Low dose artichoke +HFD: after induction of obesity for 8 weeks, rats received artichoke water extract (low dose, 600 mg /kg body weight /day) in distilled water orally by gavages for 3 weeks.
(4) High dose artichoke +HFD: after induction of obesity for 8 weeks, rats received artichoke water extract (high dose, 1500 mg /kg body weight /day) in distilled water orally by gavages for 3 weeks.

Sample collection:

At the end of the experimental duration (after 11 weeks), rats were fasted, scarified under ether anesthesia, blood samples were collected and serum was separated then centrifuged at 4000 r.p.m for 20 minutes. Rat organs (liver, kidney, heart) were directly removed, rinsed with ice cold saline and weighted.

Biochemical Analysis

Total lipids (TL), total cholesterol (TC), total triglycerides (TG) and high-density lipoprotein-cholesterol (HDL) were determined using commercial kits (Crescent Diagnostic, KSA). While, very low density lipoprotein (vLDL) was determined according to Norbert [6] formula: VLDL = TG/5. Meanwhile, calculation of serum LDL-Cholesterol fraction concentration was determined according to Friedewald et al. [7] formula. Alanine transaminase (ALT) and aspartate transaminase (AST) activities were determined by commercial kits (Crescent Diagnostic, KSA)**.** Superoxide Dismutase (SOD), Glutathione (GSH) and Malondialdehyde (MDA) were determined by commercial kits from (BIO Viton, USA). Total Antioxidant Capacity (TAC), Catalase (CAT), nitric oxide (NO), total bilirubin and Direct -indirect bilirubin were determined by commercial kits purchased from Bio-Diagnostic, ARE. Body mass index (BMI) was determined according to the formula: (BMI)=body weight(kg)/length $(m)^2$. RNA extraction and RT-qPCR gene expression of Lipoprotein lipase LPL were from Qiagen, USA.

Histopathological analysis

Liver tissues from right ventral lobe and the adipose tissue were fixed in 10% buffered formaldehyde, embedded in paraffin, sectioned and mounted in slides based on standard hematoxylin-eosin protocols.

Statistical analysis

Data were analyzed statistically using SPSS version 20.0 statistical packages, by means of one-way ANOVA test.

RESULTS

Biochemical Findings:

Table (1) shows high fat diet caused a significant increase in body weight causing the induction of obesity after 9 weeks of treatment; similarly, there was a significant increase ($p \leq 0.05$) in relative weight of organs (liver, kidney and heart) of HFD fed rats in comparison with control rats. Additionally, treatment by artichoke water extract either in high or low dose, reduced body weight gain and organs' relative weight.

Table 1: Effect of artichoke leaves water extract on body weight gain, relative organs weight and BMI of rats fed HFD.

Groups	Body weight gain (g)	Relative weight of liver	Relative weight of Heart	Relative weight of Kidney	Body mass index (BMI)
control	110.7±4.2 ^{a}	3.54±0.47^{a}	0.401±0.02^{a}	0.49±0.03 ^{a}	0.55±0.11 ^{a}
High fat diet (HFD)	212.7±3.4^{b}	3.92±0.41^{b}	0.485±0.3^{b}	0.54±0.05 ^{b}	0.92±0.05 ^{b}
Low dose +HFD	186±4.9 ^{c}	3.41±0.62^{b}	0.389±0.3^{c}	0.51±0.05^{c}	0.72±0.08 ^{c}
High dose +HFD	196.3±4.1^{d}	3.47±0.44^{b}	0.394±0.29 ^{c}	0.54±0.04^{b}	0.80±0.04 ^{d}

Data are expressed as mean ± S.D, means that have similar letters are not significant at ($p \leq 0.05$)

As presented in **Table (2)**, the results of this research revealed that feeding high fat diet significantly enhanced lipid parameters as compared to control group. While treatment with either low dose or high dose of artichoke water extract reduced total lipids, total cholesterol and triglycerides in rats fed HFD. Total lipid content of (low dose+HFD) group, revealed no significant ($p \leq 0.05$) difference as compared to control group, meaning that total lipid results of low dose group were restored to be near healthy control one. Same results were obtained for TG level that artichoke extract treatment decreased the level when compared to HFD group. There was a significant ($p \leq 0.05$) increase in LDL-c level which was counteracted after artichoke supplementation. It was noticed that artichoke extract did not decrease the HDL-c level that was previously increased by high fat diet. For VLDL-c result, no significant ($p \leq 0.05$) difference was observed between low dose+HFD and high dose+HFD rat treated groups.

Table (3) showed that high fat diet affects both serum ALT and AST as it increases their levels significantly ($p \leq 0.05$) as compared to control. After treatment, there is significant difference between HFD group and low dose +HFD or high dose+HFD. HFD supplementation increased total bilirubin and direct bilirubin significantly ($p < 0.05$) as compared to control. While treatment with artichoke water extract either in low dose +HFD or high dose+HFD reducedsignificantly indirect and direct bilirubin at $p < 0.05$. Total bilirubin content of low dose group, showed no significant difference at $p \leq 0.05$ when compared to HFD rats.

Table 2: Effect of supplementing artichoke extract on Lipid profile of rats fed HFD

Groups	Total lipid mg/100ml	TG mg/dl	LDL mg/dl	VLDL mg/dl	HDL Mg/dl	Cholesterol mg/dl
Control	437.8±11.3^{a}	56.6±5.4^{a}	22.8±0.7^{a}	11.3±1.0^{a}	64.0±3.2^{a}	71.16±.68^{a}
High fat diet (HFD)	629.5±16.2^{b}	78.4± 0.96^{b}	44.4±2.7^{b}	15.69± 0.19^{b}	53.3±1.4^{b}	114.2±1.6^{b}
Low dose +HFD	451.5±13.1^{a}	59.1±1.1^{a}	24.1±1.8^{a}	14.4± 0.22^{b}	58.5±9.0^{c}	79.2±1.0^{c}
High dose +HFD	527.4±26.5^{d}	66.5±0.71^{bc}	34.0±2.2^{c}	15.11±0.14^{b}	55.7±2.5^{b}	90.9±3.4^{d}

Data are expressed as mean ± S.D, means that have similar letters are not significant at $p \leq 0.05$.

Table 3: Effect of supplementing artichoke extract on liver enzyme and function of rats fed HFD

Groups	ALT U/L	AST U/L	Total bilirubin(mg/dl)	Direct bilirubin(mg/dl)	Indirect bilirubin(mg/dl)
Control	24.85 ± 1.6^{a}	64.5 ± 1.6^{a}	2.36 ± 0.23^{a}	1.60 ± 0.29^{a}	0.76 ± 0.51^{a}
High fat diet (HFD)	56.34± 1.7^{b}	114.1± 2.63^{b}	4.36 ± 0.18^{b}	3.62 ±0 .27b	1 ± 0.31^{b}
Low dose +HFD	36.35± 2.26^{c}	82.13 ± 1.07^{c}	4.38 ± .22^{b}	2.52 ± 0.30^{c}	1.37 ± 1.4^{c}
High dose +HFD	54.18 ± 1.9^{b}	92.18± 1.05^{d}	3.27 ± .18^{c}	3.17 ±0 .07^{b}	1.17 ± .09^{b}

The data are expressed as mean ± S.D, means that have similar letters are not significant at $p \leq 0.05$.

Serum levels of antioxidant parameters SOD, CAT, MDA, GSH, NO and TAC were determined, and as shown in **Table 4** the high-fat diet caused a significant elevation in serum MDA, but a decline in SOD, GSH, CAT, NO and TAC levels compared to control group. This elevated levels of MDA were reduced significantly ($p < 0.05$) by 52.9% and 39.8% after administration of either low or high dose of artichoke water extract, respectively. Comparing results of all the experimental rat groups, it was shown that, SOD activity increased by 26.6% and

20.8%, GSH level by 39.3% and 17.2%, CAT activity by 20.9% and 7.6%, NO level by 26% and 6.4% and TAC by 107% and 46% for low and high dose of artichoke leaves water extract respectively, as compared to high fat diet HFD.

Table 4: Effect of supplementing artichoke extract on lipid peroxidation, non-enzymatic and enzymatic antioxidants in all experimental groups

Groups	SOD (U/mg)	CAT (U/L)	TAC (mM/L)	MDA (nmol/mg)	NO (µmol / L)	GSH (nmol/mg)
Control	12.43±0.19 [a]	148.0±12.2[a]	0.52±0.04 [a]	0.57±0.02 [a]	16.65±0.8 [a]	5.89±0.09 [a]
High fat diet (HFD)	7.7±0.32 [b]	102.7± 3.5 [b]	0.13±0.03 [b]	1.53±0.15 [b]	11.52±0.7 [b]	3.25±0.12 [b]
Low dose +HFD	9.8±0.13 [c]	124.5±5.1 [c]	0.27±0.02 [c]	0.72±0.2 [c]	14.52±0.5 [c]	4.53±0.08 [c]
High dose +HFD	9.35*±0.06 [d]	110.6±9.2 [d]	0.19±0.01[d]	0.92±0.1 [d]	12.26±0.5 [d]	3.81±0.09 [d]

Data are expressed as mean: ± S.D means that have similar letters are not significant at p≤0.05.

Liver Histopathological findings:

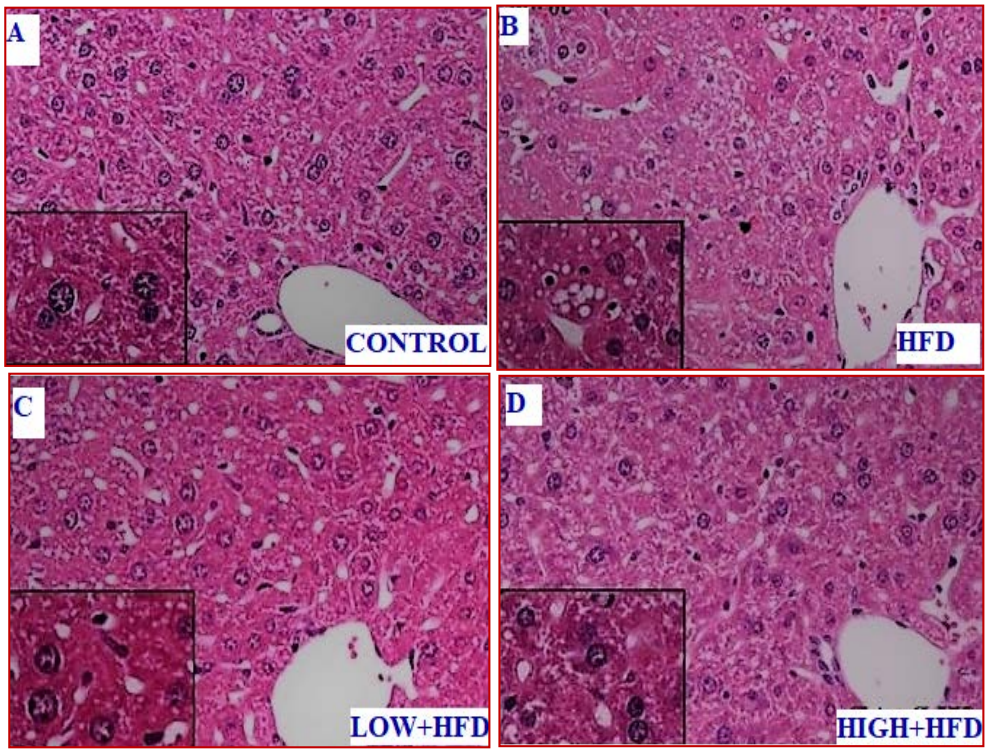
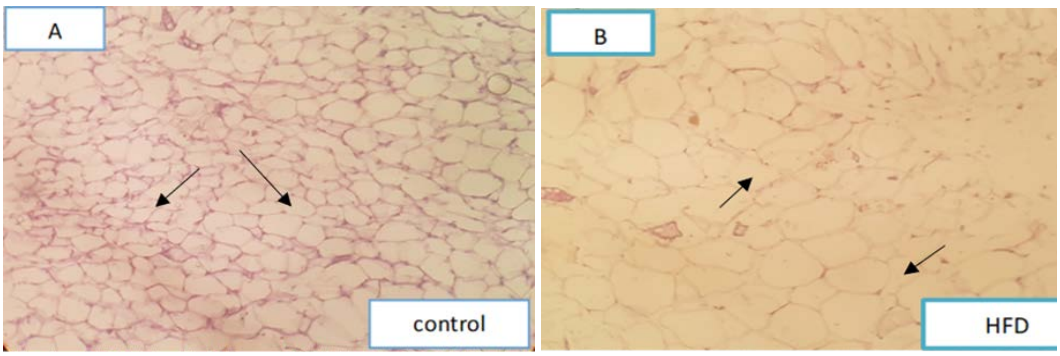


Figure 1: Histopathological features of liver samples in all experimental groups (A) control group, normal liver cells show cells in normal arrangement, (B) HFD group show accumulation in fat droplets between liver cells (C) Low+HFD group show a decrease in fat droplets between liver cells in comparison with HFD group (D) High+HFD group show fat droplets that were slightly lower than low+HFD group.

Adipose tissue Histopathological Findings



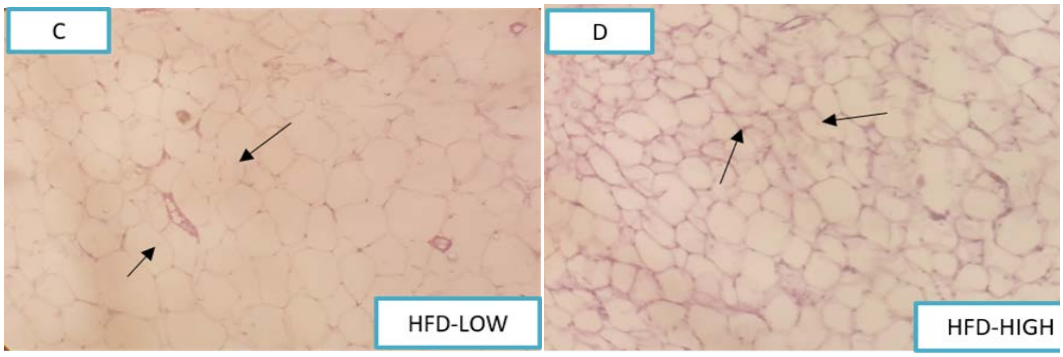


Figure 2: Features of adipose tissues' samples in all experimental groups **(A)** control group, normal adipose tissues, cells in normal arrangement **(B)** HFD group, increased number and size of adipose tissues **(C)**Low+HFD group, show a reduction in the number and size of adipose tissues as compared to HFD group and slightly lower than high +HFD group **(D)**High+HFD, group shows decreased number and size of adipose tissues

Real-time polymerase chain reaction (RT-qPCR) Data Analysis of lipoprotein lipase in adipose tissue:
We calculated P value using (One-Way Anova); P value <0.05 was statistically significant (Table 5). Results of gene expression was shown in **table (6)**; there was significant reduction in the ACTB-LPL gene relation expression between all groups as compared with control at P value <0.05. There was a significant difference between low +HFD and high +HFD.

Table 5: Absolute or relative expression of target genes in each group in comparison to reference gene.

Groups	Genes (Relative Expression, RE)
	ACTB-LPL
Control	3.29^{a}
HFD	0.89^{b}
Low dose +HFD	4.80^{c}
High dose +HFD	1.01^{d}

Table 6: Relative quantification (Rq) of genes in test group while comparing any two groups, ratio of expression (Rq) = relative expression of test/ relative expression of control.

Groups Comparisons		Genes (Rq)
Control	**Test**	**LPL vs ACTB**
Control	High dose +HFD	0.31
Control	HFD	0.27
Control	Low dose +HFD	1.46

DISCUSSION

Management of enhanced lipid parameters require diet control, exercise, and using lipid-lowering compounds such as drugs and diet. So, looking for new natural compounds with lipid-lowering effects and less side effects is necessary [8].

The aim of this study was to study the role of supplementing low and high doses of water extract of artichoke leaves in HFD fed rats by determining weight gain, lipid parameters, liver enzymes and liver histological status. In the present research, artichoke was purchased as commercial leave extract. Artichoke leaves extract contain caffeoylquinic acids and luteolinglucosides,on the other hand, leave extract has been reported to show antioxidative, liver-protective, bile-expelling, anti-microbial and lipid-lowering impacts in different pharmacological test systems [5].

HFD induced obesity after 8 weeks of feeding HFD; the increase in body weight was counteracted in groups fed artichoke water extract by either low or high dose. Artichoke used as a traditional treatment for different diseases such as hyperlipidemia [1]**.**Similarly, feeding HFD was accompanied by increased serum total lipid content, while supplementing low or high doses of artichoke water extract decreases this content. HFD results in the occurrence of hyperlipidemia thus enhance non-esterified fatty acid and TG stores in non-adipose tissues, e.g. muscle, liverand pancreas [8]. Metabolites of fatty acids accumulated causing "lipotoxicity". Thus,

increased levels of triglyceride level are often coming with slight increase in total cholesterol and a noted reduction in high-density lipoprotein (HDL) cholesterol [9].

In this study, artichoke water extract supplementation triggered significant reductions in serum cholesterol and triglyceride levels of rats fed high fat diet. The mechanism of decreasing cholesterol level by artichoke leave extract was studied by examining the role of the constituent luteolin in the inhibiting effect of artichoke extract on cholesterol synthesis. It inhibits HMG-CoA reductase, the essential enzyme of cholesterol biosynthesis and prevents accumulation of undesired sterol compounds**.** These findings revealed that both caffeoylquinic acids and luteolinglucosides were responsible for its antiatherogenic activities [10]. Caffeic acid,chlorogenic acid, cynarin, and luteolin are responsible for decreasing lipid peroxidation *in vitro* experiments [11]**.** Lipid lowering effect was more apparent in low dose of artichoke water extract rather than that of high dose of artichoke extract. The results of the present study agreed with a study by Mocelin et al [12] which showed that using artichoke dose ranging from 600 mg/kg mitigated the elevated values of serum TC and LDL-C levels.

HFD caused a significant elevation in serum levels of hepatic markers ALT and AST; this was accredited to the liver injury, because these enzymes are place in cytoplasmic area of the cell and are released into circulation in case of cellular damage. Marchesini et al [13] detailed that, Obesity and overweight increased levels of hepatic enzymes ALT and AST concentration in liver and tissues. On the other hand, supplementing water artichoke extract suppressed ($p < 0.05$) the increase of serum AST and ALT activities induced after feeding HFD. Mehmetçik et al [14] examined the effect of using 1500 mg /kg of the extract that given to rats orally for 14 days and observed a significant reduction in plasma ALT and AST actions. The hepatoprotective action of artichoke may be due to its contents of bioactive compounds [15].In present study HFD increased total bilirubin which reduced after ALE supplementation. Different studies showed that obesity may affect serum total bilirubin while artichokeextract causing substantial elevation in the excreted bile and biliary acids concentrations [16]. In vitro investigations had shown that, the cynarin, chlorogenic acid, and caffeoyl derivatives are present in artichoke and protect hepatocytes. Its therapeutic activities are mostly related to the cynarin content. In our study ALE decreased total bilirubin which was more apparent in high dose of artichoke; similar results were obtained in a study by Kurt et al., [16] in which reduction of total bilirubin is persisted with high levels of artichoke.

Oxidative stress has been suggested as a contributor to obesity; indeed, an impairment of superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), and nitric oxide (NO), total antioxidant capacity (TAC) activities and reduction of glutathione level are some of obesity's manifestations. Also, non-enzymatic antioxidants appear to be negatively affected by obesity [17]. When cells are under oxidative stress, the antioxidant system responds by altering their activities [18]. Studies showed that increased lipid peroxides in cell membrane lowered the activity of SOD and CAT in hyperglycemia and hypercholesterolemia, associated with obesity and membrane damage [19]. A study by Imessaoudene et al., [20] on obese rats offered high levels of adipose (MDA); this is due to an elevated adipose protein and lipid peroxidation, and clarified by mitochondrial dysfunction and release of fatty acids by adipose tissue. There are two antioxidant mechanisms: (1) scavenging of free radicals by acting as reducing agents; (2) chelation of transition metal ions, thus reducing free radical generation [21]. The caffeoylquinic acid content of artichoke extract improved inducible (NO) synthase enzyme (iNOS) expression thus leads to increase serum nitric oxide (NO) level [22].

Administration of ALE increasedglutathione (GSH) and CAT levels; this result was similar to the study carried out by Salem et al [23]. While in a different manner another study [24] study, showed that usage of edible portion of artichoke elevated glutathione reductase activity has no effects on other antioxidant enzymes SOD and CAT.

Histopathological examination is a method that is used to evaluate the effect of medicinal plants on experimentally induced obesity in rats. In our study, biochemical findings were also confirmed by histological observations; high fat diet markedly affects adipose tissue by increasing the number and size of adipose tissues cells. However, artichoke extract might attenuate the histological damage in rat liver through its strong antioxidant properties. The adipose tissue appearance of rats treated with artichoke was improved so much to near the values of the normal control.

The biochemical results were also verified by histological observations. High fat diet markedly affected histopathological structure of hepatic cells by causing remarkable fat accumulation. Supplementation of artichoke water extract improves these histopathological findings. Adipose tissue is a biological caloric pool that

is enlarged due to over-nutrition and liberates lipids in response to energy shortage. It is responsible for accumulating excess triglycerides in their cellular lipid droplets without the common lipotoxicity practiced by other cells [25]. Measuring lipoprotein lipase (LPL) gene expression indicated that our work explored the ability of modulating adipose tissue lipase activity in addition to anti-obesity effect. Our result showed that there was elevation in lipoprotein lipase. Ma et al [26] in their study explored gene expression of hormone sensitive lipase and lipoprotein lipase in obesity-prone and obesity-resistant rats induced by high-fat diet, indicating the relation between high levels of the enzyme and obesity.

CONCLUSION

Our findings indicated that artichoke water extract could be helpful as dietary supplement in case of obesity induced by hyperlipidemic diet. This may be due to its bioactive compounds that have beneficial effects in reducing body weight gain, controlling serum lipid abnormalities and improving liver enzymes.
Moreover, it reduces obesity-related metabolic alterations and adipose tissue fat accumulation via its protective role against reactive oxygen species induced from high fat diet.

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