

Biological Effect of *Cynara cardunculus* on Kidney Status of Hypercholesterolemic Rats

Abdullah Gilil Alkushi

Department of Anatomy, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

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ABSTRACT

Context: *Cynara cardunculus* or artichoke thistle belongs to the sunflower family and has a variety of cultivable forms. Historically, it was cultivated as a vegetable, but more recently, it is being used in cheese and biofuel preparation. Artichoke leaf extracts are also known for its medicinal purposes, particularly in reducing the elevated cholesterol levels in blood. Hypercholesterolemia (HC) is also associated with other complications such as impaired renal function and diabetes mellitus. A remedy without major side effects for HC and its associated complications is highly desirable. **Aims:** We explored the effect of artichoke on the kidneys of hypercholesterolemic adult male Sprague–Dawley albino rats. **Subjects and Methods:** Oral administration of 200 mg/kg and 400 mg/kg body weight (b.wt.) of *C. cardunculus* leaf extract (CCL) and *C. cardunculus* pulp extract (CCP) was made to male Sprague–Dawley albino hypercholesterolemic rats and investigated the levels of glucose, creatinine, uric acid, and urea in their blood. **Results:** We observed that both CCL and CCP significantly reduced the creatinine and uric acid levels in the blood in a dose-dependent manner ($P < 0.05$). Both CCL and CCP significantly reduced the blood glucose levels ($P < 0.05$). Further, the histopathological investigation of the kidney sections showed that CCL treatment resolved HC-associated kidney damage. **Conclusion:** CCL not only has cholesterol-reducing capacity but also reduces the blood glucose levels and repairs the impaired kidney functions and damages. These findings are significant particularly because HC results in further complications such as diabetes and kidney damage, both of which can be treated effectively with artichoke.

Key words: *Cynara cardunculus*, histopathology, hypercholesterolemia, kidney, kidney, rat

SUMMARY

• *C. cardunculus* leaf extract (CCL) not only has cholesterol-reducing capacity but also reduces the blood glucose levels and repairs the impaired kidney functions and damages. This study evaluated the nephroprotective role of CCL and CCP in hypercholesterolemic rats and observed that both CCL and CCP significantly reduced the creatinine

and uric acid levels in hypercholesterolemic rats in a dose-dependent manner.



Artichoke is beneficial against hypercholesterolemia-associated renal damage and elevated blood glucose levels.

Abbreviations used: HC: Hypercholesterolemia, WHO: World Health Organization, BAS: Bile acid sequestrant, PCSK9: Proprotein convertase subtilisin kexin type 9, ALE: Artichoke leaf extract, CCL: *Cynara cardunculus* leaf extract, CCP: *Cynara cardunculus* pulp extract, BWG%: Body weight gain %, FER: Food-efficiency ratio.

Correspondence:

Dr. Abdullah Gilil Alkushi,
Department of Anatomy, Faculty of Medicine,
Umm Al-Qura University, Makkah 21955,
Saudi Arabia.
E-mail: dr.alkushi@gmail.com
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INTRODUCTION

Hypercholesterolemia (HC) is defined as the increase in the levels of cholesterol in the blood. As per the recommendation of the expert panel of National Cholesterol Education Program, the desirable blood cholesterol levels should be <200 mg/dL. Levels ranging between 200 and 239 mg/dL are considered as borderline for cholesterol levels, and individuals with blood cholesterol level above 240 mg/dL are considered hypercholesterolemic.^[1] HC occurs due to both environmental and genetic factors.^[2] According to familial HC, environmental factors mainly include obesity and diets rich in saturated fats, whereas genetic factors comprise the additive effects of several genes or defects in a single gene.^[3-5]

Elevated cholesterol level in the blood not only causes coronary heart disease but also can lead to stroke and damage to the brain.^[6,7] High cholesterol has also been linked to peripheral vascular disease, in which

fat is deposited mainly in arteries that lead to the legs and feet.^[8] HC is also linked to Type 2 diabetes and hypertension.^[9,10]

According to the World Health Organization, increased cholesterol levels resulted in nearly 2.6 million deaths in 2004.^[11] The prevalence of HC in the Gulf region ranges from 17% to 54.9% in males and 9% to 53.2% in females, with no difference between urban and rural populations.^[12] According to

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a recent study in Saudi Arabia, more than a million Saudis have HC, and approximately 700,000 are unaware of their disease.^[13] The study further revealed that the risk of HC increased with age progression, margarine consumption, obesity along with a history of hypertension and diabetes.

Statins are effective in lowering the lipid levels in familial hypercholesterolemic patients.^[14] Ezetimibe, inhibiting the absorption of cholesterol by the intestines, is a drug that successfully counters high cholesterol levels when used in combination with statins.^[15] However, statins have a wide array of side effects ranging from mild cognitive impairment to muscle complications and an increased risk of diabetes.^[16] Ezetimibe has demonstrated no significant side effects; however, it is contraindicated in patients with active liver disease. In addition, bile acid sequestrants (BASs) such as questran, colestipol, and colesevelam have been approved for usage in controlling HC.^[17] Two monoclonal antibodies that inhibit proprotein convertase subtilisin kexin type 9 (PCSK9) are also prescribed to lower low-density lipoprotein (LDL) cholesterol levels.^[15] However, like statins, BAS and PCSK9 inhibitors also have side effects and contraindications.

In addition to drugs as therapeutic option, clinicians advise hypercholesterolemic patients to undergo lifestyle changes, such as avoiding smoking, regular exercise, and consuming a diet that is rich in fiber and low in transaturated and saturated fats.^[18] There are also certain plant products, such as the gum residue guggulipid, which are used in India as a traditional medicine to reduce blood cholesterol levels.^[19] Similarly, red yeast rice and rice bran oil have been observed to reduce elevated cholesterol levels.^[20] Other herbal products have also been investigated for their role in lowering down the cholesterol levels including fenugreek seeds and leaves, holy basil, flaxseed oil, and various other herbs and spices such as ginger and turmeric.

Another herbal remedy available for reducing high cholesterol level is the leaf extract of *Cynara scolymus*, commonly known as artichoke thistle. *Cynara cardunculus var. scolymus*, or globe artichoke, is mainly cultivated as a food crop. It is a perennial plant that is largely native to the Mediterranean region in Southern Europe, Northern Africa, and the Canary Islands. In addition to food, artichoke is used in tea and liqueur preparation. Studies on the medicinal properties of artichoke have been continuing over the last six decades. Several *in vitro* and *in vivo* studies have investigated the effect of artichoke leaf extract (ALE), especially cymarine, in reducing plasma cholesterol levels.^[21-23] Along with cymarine, the antiatherosclerotic effects of luteolin-rich artichoke extract reduces the LDL oxidation in a dose-dependent manner.^[24] A dose-dependent inhibition of cholesterol biosynthesis, using ALE, was also shown in primary cultured rat hepatocytes.^[25]

In addition to the *in vitro* and *in vivo* studies, randomized controlled studies have assessed effects of the oral administration of ALE in hypercholesterolemic patients. Bundy *et al.* assessed the effect of ALE on plasma lipid levels and general well-being in healthy individuals with mild to moderate HC.^[26] The participants of the study received 1280 mg of ALE daily (four tablets of 320 mg) for 12 weeks. The majority of participants were females, and nearly 90% of them were more than 40 years old. The plasma cholesterol levels were found to be reduced by 4.2% in the group administered ALE, whereas they increased by 1.9% in the placebo group. No significant difference in LDL cholesterol, high-density lipoprotein cholesterol, or triglycerides was observed between the groups. Englisch *et al.* conducted a similar study among 18–70-year-old hypercholesterolemic patients.^[27] In addition to treatment with cholesterol-reducing drugs, participants were prohibited from antibiotic treatments. The intervention group received 1800 mg of ALE for 6 weeks. The total cholesterol levels were reduced by 18.5% in the group administered with ALE as compared to the 8.6% reduction in the placebo group.

In addition to atherosclerosis, HC can affect organs such as kidneys. Studies in rats have shown that cholesterol can increase the incidence

of glomerulosclerosis, and *in vitro* cell culture studies using human glomerular cells revealed about the possible mechanisms that are involved in the lipid influenced glomerular damage.^[28] Another study showed that treating HC in obese rats reduced their glomerular injuries.^[29] Similar observations have also been made in studies with humans. Individuals with high triglycerides or a lecithin-cholesterol acyltransferase deficiency gradually developed renal failure due to glomerulosclerosis.^[30]

Because HC can cause renal damage and medical interventions for HC treatment have adverse effects and contraindications, herbal remedies such as ALE are very promising for treating elevated cholesterol levels. Despite the limited availability of scientific literature on the effect of artichokes on kidney function, several health forums have advised for artichoke consumption to treat kidney damage. Based on a previous report on reduced cholesterol levels treating renal injury, we investigated whether ALE treatment in hypercholesterolemic rats could treat kidney damage.

SUBJECTS AND METHODS

In this study, we investigated the effect of artichoke on the kidneys of hypercholesterolemic adult male Sprague–Dawley albino rats and induced HC in rats by feeding them a cholesterol-rich diet for 2 weeks. Later, the rats were grouped and treated with either *C. cardunculus* leaf extract (CCL) or *C. cardunculus* pulp extract (CCP) at 200 or 400 mg/kg b.wt. or fed a basal diet. CCL treatment administered with 400 mg/kg b.wt. significantly reduced the creatinine, uric acid, and urea levels, whereas similar dose of CCP reduced creatinine and uric acid levels in comparison to untreated hypercholesterolemic rats ($P < 0.05$). CCP treatment administered with the 200 mg/kg b.wt. dose significantly ($P < 0.05$) reduced the levels of creatinine and uric acid, but the same dose of CCL only reduced uric acid. No significant change was observed in the ratio of kidney to body weight (b.wt.) of the rats in the treatment groups except hypercholesterolemic rats treated with CCL at 400 mg/kg b.wt. dose. Histological examination of the kidneys from rats treated with CCP neither showed hypercellularity of the glomerular tuft nor necrobiotic changes in tubular epithelial lining that was clearly visible in untreated hypercholesterolemic rats, which supported the role of CCP in repairing cholesterol-induced kidney damage in rats. Treatment with CCP and CCL significantly reduced blood glucose levels in hypercholesterolemic rats. Using an *in vivo* rat model for HC, we show that *C. cardunculus* (artichoke) can reverse the cholesterol-induced kidney damage in a dose-dependent manner.

Plants

Artichoke (*C. cardunculus var. scolymus*) was purchased from a local market at Makkah, Saudi Arabia.

Preparation of aqueous extracts

Artichoke was grounded using a porcelain grinder and passed through mesh with pores 1 mm in diameter. Plant extract was prepared as described previously,^[31] i.e., 1 g of powdered leaves was mixed with 100 ml distilled water that was later boiled for 10 min and left to cool for 15 min. This aqueous extract was subsequently filtered using 0.2 mm filter paper to remove particulates. Furthermore, the filtrate was dried (lyophilized) and reconstituted in 1.5 ml of distilled water (100 mg/kg b.wt.).

Experimental animals

Sixty adult male Sprague–Dawley albino rats, having 190 ± 10 g of average b.wt., were obtained from the Laboratory Animal Centre, Department of Anatomy, Faculty of Medicine, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia (KSA). Experiments were carried out in the animal house facility at the Faculty of Medicine, Umm Al-Qura University, where the animals were housed in clean polypropylene cages. There were

no more than four animals per cage, and the cages were maintained under standard laboratory conditions, i.e., 25°C ± 2°C temperature and 12-h dark-light cycle. Animals were acclimated to laboratory conditions for 1 week before experiments. All the above-described procedures were reviewed and approved by the Animal Care and Use Bioethical Committee of Medical Sciences, Umm Al-Qura University, KSA.

Basal diet

The composition of the basal diet (in g/100 g) for normal and hypercholesterolemic rats is shown in Table 1. The salt and vitamin mixture composition was as according to the descriptions in the study by Hegested *et al.*^[32] and Campbell,^[33] respectively.

Cholesterol

Cholesterol was obtained as a pure white crystalline powder from Sigma-Aldrich, St. Louis, MO, USA.

Induction of hypercholesterolemia in rats and experimental design

During acclimatization, all rats were fed a basal diet for 1 week before the initiation of experiments. After the 1-week period, rats were divided into two main groups. The first group was referred as GI and consisted of 10 rats that were fed with only the basal diet. Rats in GI group were healthy and served as the negative control in this study. To induce HC in the remaining 50 rats, the basal diet was supplemented with 2% cholesterol for 2 weeks before experiments. After 2 weeks on the supplemental diet, all 50 rats were divided into five groups of 10 rats each based on the treatments categories. The GII group comprised rats that continued on the standard basal diet and represented as a positive control. In addition to the basal diet, the rats of GIII and GIV groups were orally administered with CCL once daily at 200 mg/kg and 400 mg/kg b.wt. doses, respectively. Rats in GV and GVI groups received an oral extract of CCP at 200 mg/kg and 400 mg/kg b.wt., respectively, along with the basal diet.

At the end of the experiment, the impact of the diverse diets was evaluated by calculating the body weight gain% (BWG%) and food efficiency ratio (FER) of the rats, as described by Chapman *et al.*^[34] All rats were weighed once a week.

Blood collection and organs sampling

Blood samples were collected by sacrificing the rats 24 h after the last feed after anesthetizing them in a chamber containing diethyl ether. Two blood samples, one in heparin and one in a plain tube, were collected from each rat. For serum collection, plain tubes containing blood were centrifuged at 3000 rpm for 10 min. Clear supernatant serum was collected and stored at -20°C until further analysis.

Biochemical analysis

Spectrophotometric estimations of fasting blood glucose, uric acid, urea, and creatinine levels were performed using commercial kits (Crescent Diagnostics, Jeddah, KSA) as per the manufacturer's protocol.

Tissue specimen collection and histopathological examination

Kidney specimens were collected from rats in all experimental groups at the end of the experiment. The collected specimens were immediately fixed in 10% formalin. After proper fixation, specimens were dehydrated in ethyl alcohol, cleared in xylol, and embedded and cast in paraffin. Thin paraffin sections were prepared and stained with hematoxylin and eosin as previously described.^[35] Histological examinations were performed

in a pathology laboratory at the Faculty of Medicine, Umm Al-Qura University, Saudi Arabia.

Statistical analyses

Statistical analyses used SPSS version 20 for Windows (The IBM®, USA). All values are expressed as the mean ± standard deviation. Paired-sample *t*-tests between control, positive, and hypercholesterolemic rats groups were used to compare all parameters. A *P* < 0.05 was considered statistically significant. Parameters for the GII group were compared to those of the GI, GIII, GIV, GV, and GVI groups. *P* ≤ 0.05, *P* ≤ 0.01, and *P* < 0.001 are referred as significant, highly significant, and very highly significant and were represented as *, **, and ***, respectively.

RESULTS

Effect of *Cynara cardunculus* on fasting glucose levels in hypercholesterolemic rats

The mean fasting glucose levels in healthy rats fed a basal diet (GI) were significantly lower (*P* ≤ 0.01). The glucose levels in hypercholesterolemic rats (GII) treated with CCL at doses of 200 and 400 mg/kg b.wt. were 143.81 ± 17.54 and 129.84 ± 20.32, respectively, and were significantly lower (*P* < 0.05) than those in the hypercholesterolemic rats fed on a basal diet [Table 2]. Similarly, compared to GII group, the fasting glucose levels were significantly lower (*P* < 0.05) in hypercholesterolemic rats of GVI group that were administered with CCP at 200 and 400 mg/kg b.wt. In rats treated with 400 mg/kg b.wt. of both CCL and CCP, they had lower levels of serum glucose levels as compared to rats treated with a dose of 200 mg/kg [Table 2].

Effect of *Cynara cardunculus* on kidney function in hypercholesterolemic rats

Table 3 shows the levels of creatinine, uric acid, and urea levels among different treatment groups. The creatinine levels in hypercholesterolemic rats treated with CCL in doses of 200 and 400 mg/kg b.wt. were reported to be 0.46 ± 0.008 mg/dl and 0.46 ± 0.008 mg/dl, respectively, which was significantly lower (*P* < 0.05) than those in untreated hypercholesterolemic rats (GII). However, a significant reduction in creatinine level was observed only in rats treated with CCP at 400 mg/kg b.wt. of dose [Table 3]. Similarly, the uric acid levels were significantly

Table 1: Diet composition (g/100 g) of normal and hypercholesterolemic rats

Casein (%)	Corn oil (%)	Vitamin mixture (%)	Salt mixture (%)	Starch (%)
12	10	1	4	up to 100

Table 2: Effect of *Cynara cardunculus* on fasting serum glucose levels (mg/dL) of hypercholesterolemic rats

Groups	Extracts	Doses (mg/kg b. wt.)	Glucose
Control negative			
Group I	-	-	101.14±12.42**
Control positive			
Group II	-	-	162.61±11.66
Treated groups			
Group III	CCL	200	143.81±17.54*
Group IV	CCL	400	129.84±20.32**
Group V	CCP	200	147.98±22.22*
Group VI	CCP	400	130.55±12.31**

P ≤ 0.05 and *P* ≤ 0.01 are referred as significant and highly significant and are represented as * and ** respectively. CCL: *Cynara cardunculus* leaf extract; CCP: *Cynara cardunculus* pulp extract; b.wt.: Body weight

Table 3: Effect of *Cynara cardunculus* on serum creatinine, uric acid, and urea levels (mg/dL) in hypercholesterolemic rats

Groups	Extracts	Doses (mg/kg b.wt.)	Creatinine	Uric acid	Urea
Control negative Group I	-	-	0.45±0.005	2.75±0.049***	23.47±1.23**
Control positive Group II	-	-	0.56±0.013	6.27±0.083	32.09±3.02
Treated groups					
Group III	CCL	200	0.46±0.008*	4.95±0.007*	28.57±3.98
Group IV	CCL	400	0.35±0.004**	4.49±0.006**	25.29±2.31*
Group V	CCP	200	0.55±0.005	4.47±0.019**	30.09±4.18
Group VI	CCP	400	0.53±0.0*	3.95±0.008**	29.96±3.57

$P \leq 0.05$, $P \leq 0.01$, and $P < 0.001$ are referred as significant, highly significant, and very highly significant and were represented as *, **, and ***, respectively. CCL: *Cynara cardunculus* leaf extract; CCP: *Cynara cardunculus* pulp extract, b.wt.: Body weight

reduced in all hypercholesterolemic treated groups (GIII–GVI) as compared to the untreated hypercholesterolemic group (GII). In contrast, the urea levels significantly reduced ($P < 0.05$) in rats treated with CCL only at 400 mg/kg b.wt. of dose (GIV) and the mean urea level was 25.29 ± 2.31 mg/dl in GIV group and 32.09 ± 3.02 mg/dl in the untreated hypercholesterolemic group (GII).

Effect of *Cynara cardunculus* on kidney to body weight ratio in hypercholesterolemic rats

The mean kidney:b.wt. ratio [Table 4] among healthy (GI) and hypercholesterolemic (GII) rats fed on basal diet were 0.591 ± 0.006 and 0.532 ± 0.012 , respectively, and the difference was statistically significant ($P < 0.05$). However, the kidney:b.wt. ratio of the rats was not significantly different for hypercholesterolemic groups and the rats that were treated with 200 mg/kg b.wt. of CCL (GIII) or CCP (GV) or 400 mg/kg b.wt. CCP (GVI) as compared to the hypercholesterolemic group (GII) fed only a basal diet ($P > 0.05$). However, hypercholesterolemic rats treated with 400 mg/kg b.wt. of CCL (GIV) had a significantly lower the kidney:b.wt. ratio as compared to hypercholesterolemic rats fed a basal diet (GII).

Effect of *Cynara cardunculus* on body weight gain and food efficiency ratio of hypercholesterolemic rats

The biological effect of *C. cardunculus* on BWG and FER of hypercholesterolemic rats after 6 weeks of feeding is shown in Table 5. Concerning the BWG% in rats of GIII, GIV, and GVI groups, it was found that a significant decrease ($P < 0.05$) was recorded as compared to the control positive group. The mean values were 58.33 ± 6.72 , 55.3 ± 5.55 , 70.22 ± 7.83 , and 59.33 ± 6.32 , respectively. It is evident that lowest value of BWG% was found for GIV rats that were fed on CCL 400 mg/kg b.wt. The same trend was observed for FER, and there was a significant difference ($P < 0.05$) in GIV rats as compared to the rats on cholesterol diet (0.037 ± 0.0028 and 0.044 ± 0.00075). In the rats of both the treated groups, FER was higher than that of the control negative group.

Histopathological examination of kidneys following *Cynara cardunculus* leaf extract and *Cynara cardunculus* pulp extract treatment

Kidney sections of the rats fed with basal diet, i.e., the negative group (GI), showed normal histological structures for glomeruli and tubules [Figure 1]. In contrast, the kidney sections from the rats fed with basal diet and 2% cholesterol for 2 weeks showed hypercellularity of the glomerular tuft, necrotic changes in the tubular epithelia lining, and intraluminal albumin droplets [Figure 2].

Table 4: Biological effect of *Cynara cardunculus* on kidney to body weight ratio of hypercholesterolemic rats

Groups	Extracts	Doses (mg/kg b.wt.)	Kidney (g/100 g b.wt.)
Control negative Group I	-	-	0.591±0.006*
Control positive Group II	-	-	0.532±0.012
Treated groups			
Group III	CCL	200	0.571±0.023
Group IV	CCL	400	0.562±0.091*
Group V	CCP	200	0.583±0.005
Group VI	CCP	400	0.571±0.011

* $P \leq 0.05$. CCL: *Cynara cardunculus* leaf extract; CCP: *Cynara cardunculus* pulp extract; b.wt.: Body weight

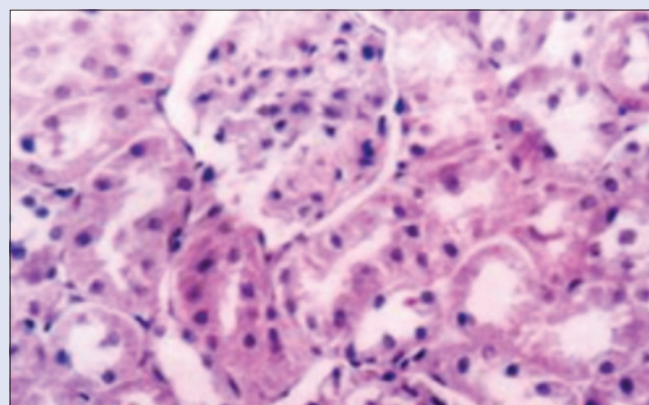


Figure 1: Hematoxylin and eosin-stained paraffin embedded kidney sections at $\times 100$ magnification of healthy rats

Among the hypercholesterolemic rats treated with 200 mg/kg b.wt. CCL (GIII), the histological examination of their kidney sections showed dilated tubules containing hyaline material in the lumen [Figure 3]. Similar histology was observed in the kidney sections of rats of GIV group administered with 400 mg/kg b.wt of CCL [Figure 4].

However, rats treated with CCP at doses of 200 mg/kg (GV) and 400 mg/kg (GVI) showed hypercellularity of the glomerular tuft and necrobiotic changes in tubular epithelial lining with intraluminal albumin droplets [Figures 5 and 6].

DISCUSSION

If not controlled, HC can lead to atherosclerosis which can further head for stroke. In addition to atherosclerosis, HC can lead to other complications, such as diabetes and kidney damage. Several drugs

Table 5: The effect of *Cynara cardunculus* on body weight gain 1 and food efficiency ratio 2 of hypercholesterolemic rats

Groups	Extracts	Doses (mg/kg b.wt.)	BWG	FER
Control negative Group I	-	-	47.26±3.85**	0.022±0.0021**
Control positive Group II	-	-	81.46±7.52	0.044±0.00075
Treated groups				
Group III	CCL	200	58.33±6.72*	0.041±0.0006
Group IV	CCL	400	55.3±5.55*	0.037±0.0028*
Group V	CCP	200	70.22±7.83	0.044±0.0029
Group VI	CCP	400	59.33±6.32*	0.042±0.0030

$P \leq 0.05$ and $P \leq 0.01$ are referred as significant and highly significant and are represented as * and ** respectively. BWG: Body weight gain; FER: Food efficiency ratio; CCL: *Cynara cardunculus* leaf extract; CCP: *Cynara cardunculus* pulp extract, b.wt.: Body weight

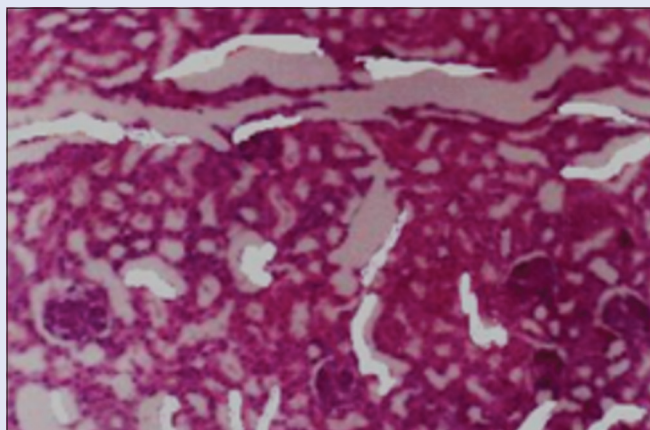


Figure 2: Hematoxylin and eosin-stained paraffin embedded kidney sections of hypercholesterolemic rats fed a basal diet

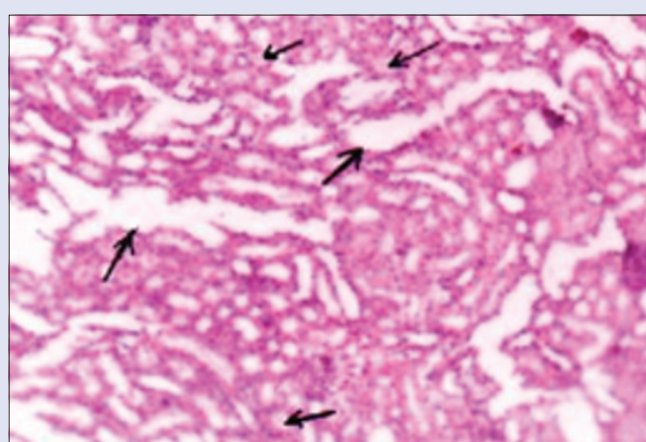


Figure 3: Hematoxylin and eosin-stained paraffin embedded kidney sections of hypercholesterolemic rats orally fed 200 mg/kg b.wt. *Cynara cardunculus* leaf extract

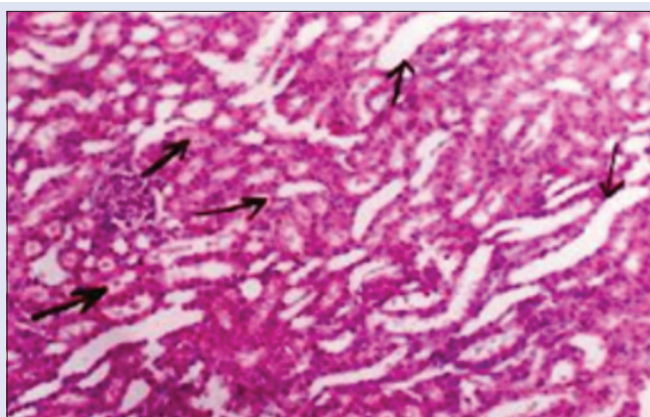


Figure 4: Hematoxylin and eosin-stained paraffin embedded kidney sections of hypercholesterolemic rats orally fed 400 mg/kg b.wt. *Cynara cardunculus* leaf extract

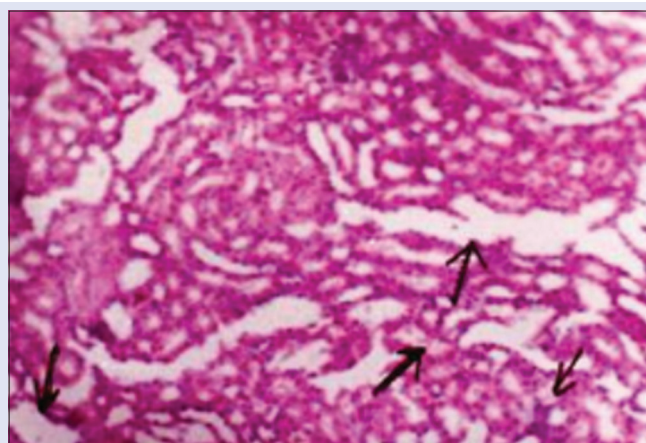


Figure 5: Hematoxylin and eosin-stained paraffin embedded kidney sections of hypercholesterolemic rats orally fed 200 mg/kg b.wt. *Cynara cardunculus* pulp extract

are being used to control cholesterol levels, and nearly all of them have shown side effects or contraindicated. A treatment that could reduce the elevated cholesterol level and repair damaged organs, such as kidneys, without causing any side effect is highly needed. *C. cardunculus* (artichoke), which has been conventionally used as a food product, is also consumed to reduce the elevated blood cholesterol levels. However, the knowledge about its effects on the kidneys of hypercholesterolemic individuals is rather limited. Therefore, we sought to investigate the role of ALE and artichoke pulp extracts on the kidneys of hypercholesterolemic rats.

Having a link with Type 2 diabetes, HC poses as a high risk in individuals with a history of diabetes.^[9,13] Therefore, we investigated whether feeding artichoke to hypercholesterolemic rats could reduce their blood sugar levels. In this study, we found that both CCL and CCP treatment led to a significant reduction in blood glucose levels as compared to the untreated hypercholesterolemic rats (GII). However, the levels remained slightly elevated in comparison to healthy mice fed on basal diet. This is

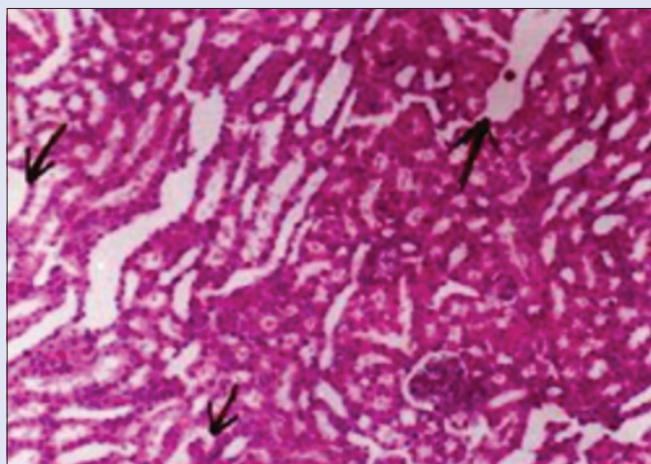


Figure 6: Hematoxylin and eosin-stained paraffin embedded kidney sections of hypercholesterolemic rats orally fed 400 mg/kg b.wt. *Cynara cardunculus* pulp extract

consistent with the previous studies showing that *C. cardunculus* L. or *C. scolymus* L. have antidiabetic properties.^[36,37] Furthermore, a recent study by Heidarian and Soofiniya showed that the ALE administration in doses of 200 and 400 mg/kg b.wt to the streptozotocin-induced diabetic rats led to a significant reduction in their blood glucose levels.^[38]

Prolonged HC can cause renal damage which leads to higher levels of creatinine, urea, or uric acid in the blood. Creatinine is a by-product of muscle contraction that is filtered from blood by the kidneys, but renal damage leads to increased levels of creatinine in the blood. Similarly, the excretion of urea and uric acid by kidneys is also a part of mammalian metabolism, and the increased concentrations of uric acid in blood are associated with other complications of HC, i.e., diabetes. We also observed that 400 mg/kg b.wt. dose of CCL reduced the elevated level of creatinine, uric acid, and urea levels significantly, while CCP administration at 400 mg/kg b.wt. reduced the blood creatinine and uric acid levels but not urea levels. Alike blood glucose results, we observed the dose-dependent effects on the kidneys of hypercholesterolemic rats. The renoprotective effect of artichoke extracts has also been observed in previous studies. A study assessed the effect of artichoke on renal dysfunction in rats and showed that the oral administration of 400 mg/kg b.wt. of artichoke leaf or head led to a significant reduction in the plasma creatinine and urea levels.^[39] In another study, the antiurolithiatic activity of ALE was investigated in rats with ethylene glycol-induced urolithiasis. Serum levels of uric acid, urea, and creatinine decreased with the administration of artichoke in a dose-dependent manner.^[40] The nephroprotective potential of artichoke has also been studied in rats with gentamycin-induced impaired renal functions. The oral administration of ALEs significantly decreased the creatinine, uric acid, and urea levels in the blood.^[41]

Body weight is an indicator of any kind of adverse effects. The ratio of the effect of artichoke on the kidney to the b.wt. of the hypercholesterolemic rats showed no significant difference between the treated and the untreated groups, except for the group treated with CCL at 400 mg/kg. The results from previous studies vary showing no differences between treated and untreated groups, but some showed a significant difference in the altered kidney:b.wt. ratios.^[40-42] It has often been observed that restoring renal function to normal condition corresponds with a nearly normal kidney:b.wt. ratio.^[40]

In addition to quantitative tests, we performed histopathological examinations of the kidney sections from animals in the treated and

untreated groups. We found a hypercellularity of the glomerular tuft and necrotic changes in tubular epithelia lining in the kidneys of the rats fed with 2% cholesterol. However, no such pathology was observed in mice receiving oral administrations of CCL at 200 and 400 mg/kg b.wt. doses, whereas CCP administration showed damaged glomeruli. Similar effects were also observed when ALE were used on kidneys that were isolated from ethylene glycol-treated rats.^[40] The histopathology of the kidneys of rats receiving intraperitoneal gentamicin showed similar damage, which was resolved in a dose-dependent manner following the ALE treatment.^[41]

CONCLUSION

This study evaluated the nephroprotective role of CCL and CCP in hypercholesterolemic rats and observed that both CCL and CCP significantly reduced the creatinine and uric acid levels in hypercholesterolemic rats in a dose-dependent manner.^[43,44] In addition, both CCL and CCP reduced the blood glucose levels significantly showing that artichoke extracts could prevent diabetes, which is a major risk factor for kidney damage. Treatment with CCL extracts resulted in no pathological damage to the kidney, whereas CCP treatment resulted in renal damage. Although CCL and CCP treatments improved the kidney function, the nephroprotective responses were far better with CCL treatment. This study shows that artichoke is beneficial not only against HC but also against HC-associated renal damage and elevated blood glucose levels.

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Conflicts of interest

There are no conflicts of interest.

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