

## Therapeutic and Preventive Effects of Aqueous Extracts of *Arctium lappa L.* and *Cichorium intybus L.* against Fatty Liver in Rats

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### Abstract

**Background and objectives:** The fatty liver is a reversible form of fat accumulation in the liver tissue. The burden of this disease is increasing worldwide. Researchers have focused on using herbal medicines due to the lack of proper treatment and numerous side effects of existing chemical medicines. This study aimed to evaluate the therapeutic effects of aqueous extract of *Arctium lappa L.* (burdock) and *Cichorium intybus L.* (chicory) on fatty liver in rats fed with a high-fat diet as these plants have been frequently applied in traditional medicine for the treatment of the liver-related diseases.

**Material and Methods:** For this study, 30 Wistar rats weighing 120-220 g were used. The rats were divided into five groups and received 125, 250, 500, and 1000 mL/kg of a mixture of aqueous extracts of burdock and chicory. The biochemical indexes, including aspartate aminotransferase, alanine aminotransferase, and etc. were analyzed. Also, for histologic examination liver tissue samples were stained with hematoxylin-eosin.

**Results:** We showed that the aqueous extract reduced the liver macro-vesicles and microvesicles and symptoms of steatosis without any specific liver complications. We also found that 500 and 1000 mL/kg of extract had the most effective therapeutic effect.

**Conclusion:** In conclusion, our study shows that extract of burdock-chicory has the potential to ameliorate fatty liver in rats fed with a high-fat diet. This study provides evidence that burdock-chicory extract could be considered a potential dietary supplement strategy for preventing and treating fatty liver.

**Keywords:** Liver [[MeSH](#)]; Aspartate Aminotransferase [[MeSH](#)]; Alanine Transaminase [[MeSH](#)], *Arctium lappa L.* (burdock); *Cichorium intybus L.* (chicory)

### Highlights

- The fatty liver is a reversible form of fat accumulation in the liver cells.
- The aqueous extract of *Arctium lappa L.* (burdock) and *Cichorium intybus L.* (chicory) reduces the liver macro-vesicles and micro-vesicles and symptoms of steatosis without any specific liver complications.
- The burdock-chicory extract could be considered a potential dietary supplement strategy for preventing and treating fatty liver.

## Introduction

Fatty liver has recently increased in our society due to increased obesity. The importance of this disease is due to the destruction of liver cells; if fatty liver is not detected in the early stages, it can lead to an irreversible liver disease called cirrhosis. According to the studies, the prevalence of the fatty liver disease is about 46%. The most common cause of this disease is elevated liver enzymes; however, the etiology of liver cirrhosis remains unknown. Studies in this field are limited in Iran. A study in the Golestan province of Iran in 2006 showed that the rate of fatty liver disease was 2% in the general population over 18 years old (1-3). Increased liver size is detectable in about 75% of patients in a clinical examination. Symptoms of chronic and progressed liver diseases, such as spider angioma, palmar erythema, abdominal fluid accumulation, and spleen enlargement, are visible in a few patients whose diagnosis is delayed. Gemfibrozil, a lipid-lowering drug, improves the laboratory symptoms of fatty liver (4). Statins, other lipid cholesterol-lowering drugs, also improve the laboratory symptoms (5), while ursodeoxycholic acid, a hepatocyte protecting agent, has not been beneficial in recent studies (6). Three major causing factors of fatty liver have been recognized, including fatty acids chemical mediators called TNF $\alpha$  and adiponectin (7). The causes of the disease can be divided into two general groups. The first group is drugs and

poisons, and the second group is metabolic disorders. As limited studies have been conducted about the possible causes of this disease, it is still a long way to achieve the best treatment. According to the current knowledge, the basis of treatment is weight loss, elimination of possible drugs and poisons, and control of diabetes and lipids in the patients. Lack of proper treatment and several side effects of existing chemical drugs, including stomach bloating, stomach pains, headache, rash, and nausea or vomiting, have led to extensive research to discover herbs/plants with therapeutic potential and without side effects.

We selected two herbs, *Arctium lappa L.*, and *Cichorium intybus L.*, which have been frequently applied in traditional medicine to treat liver-related diseases (8). We evaluated the therapeutic activity of the mixture of aqueous extracts against fatty liver disease. Burdock belongs to the genus of *Arctium* in the Asteraceae family, which has medicinal value (9). This plant is commonly native to the temperate regions of Asia and Europe. According to the chemical analysis, the root of burdock contains mainly inulin, polyacetylenes, arctic acid, propionic acid, butyric acid, lauric acid, stearic acid, palmitic acid, plant hormones, tannin, polyphenolic acid, potassium carbonate and nitrate, various resins and glucoside-lappin (10). The chemical compounds in the burdock seeds include a bitter glucoside called arctin, chlorogenic acid, lapaul A and B, germacranolide. Burdock leaves contain arctiol, fukinone, fukinanolide,  $\beta$ -eudesmol, petastilone, eremophilone, and taraxasterol. It is also reported to contain lignans, including arctigenin and its glycoside arctin, which have a variety of biological activities, such as anti-cancer, anti-HIV, antioxidant and antimicrobial effects. The medicinal plant Chicory is a plant from the *Cichorium* genus in the Asteraceae family. The main origin of this plant is central Europe, the western and central parts of Asia, and North Africa. Chicory contains sodium/potassium/magnesium phosphates and sulfates, potassium nitrate, inulin, fructose, resin, chicorin and scoletin. In chemical analysis of chopped chicory leaves, water, vitamins A, B1,

B2, 2% protein, a small amount of fat, 4% sugar, and calcium were obtained. Chicory has sesquiterpene, bitter lactones, such as lactocin, lactucopicrin, chicorein (coumarin glucoside), malton (simple pyrone) and tadaxastrine (triterpene) (11-13).

Several studies demonstrated that chicory extract might be effective in the treatment of fatty liver disease. Chicory has different activities such as antihyperlipidemic, antihyperglycemic, antihepatotoxic, anti-inflammatory, antidiabetic, and antioxidant, which make it possible that chicory affects the various steps of the disease severity and progression (14-16).

The previous studies showed that burdock exhibits antioxidant, hypolipidemic, hypoglycemic, and hepatoprotective activity and can protect cells from oxidative stress and fat accumulation (17). It has been demonstrated that burdock attenuates cholesterol accumulation in the liver and serum by reducing its absorption in the intestinal tract (18). Existing studies have demonstrated that chicory and burdock have beneficial effects on liver disease, but the combination of these has not studied. In this research, we performed preliminary studies of Cassiamon formulation, a combination of chicory and burdock herbs, which affect the fatty liver disease.

## Materials and Methods

### *Plant Material*

The studied plants, burdock, and chicory were collected from northwest Iran, the provinces of Ardebil, and East Azarbaijan. They were identified and verified using a collection of Iranian herbal flora books and samples from the Herbarium Research Center of Herbs (Islamic Azad University of Tabriz, Iran). Collected samples were dried in the shade at room temperature and blended using electric grinders to obtain a powder of aerial parts of plants (19).

### *Preparation of the Extracts*

To prepare the aqueous extract, 40 g of the powdered plant was dissolved in 1000 mL of

distilled water and kept at 4 ° C for 48 hours. The extract of the plant was isolated by filtration. The extract was again extracted in 300 mL of distilled water for 24 hours under similar conditions and for the third time the remaining extract was dissolved in 100 mL of distilled water and shaken for 2 hours. Finally, the solvent was removed using a rotary evaporator, resulting in 10 g of dry extract, which was stored at 4°C for further use.

### *Investigation of the therapeutic effect of extracts on fatty liver*

To induce liver steatosis, the high-fat emulsion was used according to the method proposed by Zou et al. (20). In summary, 30 Wistar rats were divided into six groups, with five rats in each group, respectively as control group, model group, and four test groups (groups 1 to 4). Except for the control group, the other five groups were fed with high-fat diet (Table 1) and were given high-fat emulsion (10 ml/kg body weight) by gavage. Every rat in test groups 1 to 4 received 125, 250, 500, 1000 mL/kg of aqueous extracts of burdock and chicory mixture (1:1 v/v) every day for 30 days, respectively. At the same time, the control group and the model group were given the same volume of normal saline by gavage.

**Table 1.** Composition of high-fat diet

Composition	g/300 mL dH <sub>2</sub> O
Maize oil	400
Sucrose	150
Milk powder	80
Sodium Deoxycholate	10
Cholesterol	100
Tween 80	36.5
propylene glycol	31.1
vitamin mix	2.5
Sodium chloride	10
Mineral mix	1.5

After the 30th treatment, blood was collected from rat's eyeball, the serum was separated, and data of biochemical indexes, including aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Albumin (Alb), Total Bilirubin (TB), and total protein were analyzed. Rats were killed by the method of spinal cord dissection, liver of all the rats was removed, liver tissue samples were

stabilized in 10% formalin, and 4-6  $\mu\text{m}$  sections were prepared, and stained with hematoxylin-eosin for histologic examination.

### Standardization of the extracts

The aqueous extracts of burdock and chicory mixture were standardized on the chicoric acid as the main active compound by HPLC (21).

### Statistical Analysis

Data was analyzed using SPSS Statistics Version 23.0. Comparison of differences between groups was performed by the t-Test.

### Ethics in Animal

All applicable international, national, or institutional guidelines for the care and use of animals were followed, and the Animal Ethics Committee approved the study of the Academic Center for Education, Culture and Research (ACECR), Medicinal Herbal Center of Ardabil Branch, Ardabil, I.R. Iran (No. S.94.43.1404).

## Results

### Investigation of the therapeutic effect of extracts on fatty liver

The feeding of high-fat diet for 30 days effectively induced fatty liver in rats, as evidenced by the markedly increased body weight, liver weight, and serum ALT, AST, TB, and ALP, while decreasing TP and Alb (Table 2). Furthermore, hematoxylin and eosin staining results (Figure 1B) showed that steatosis was developed and numerous lipid macro-vesicles were observed in the livers of the rats fed by high-

fat diet. Based on these results, the fatty liver disease model was considered to be successfully established. Compared with the model group, different concentrations of aqueous extracts of burdock-chicory could significantly decrease levels of ALT, AST, TB, and ALP in test groups and returned to the normal level which observed in control group (Table 3), reduce the liver macro and micro-vesicles, and decrease symptoms of steatosis without specific liver complications (Figure 2). It was found that the concentrations of 500 and 1000 mL/kg of burdock-chicory extract showed the most and the concentration of 125 mL/kg showed the least effective therapeutic effect against steatosis.

### Standardization of the extracts

The quantitative determination revealed that the quantity of cichoric acid as the main active compound was about 0.038 mg/ml in the extract (Figure 3).

**Table 2.** Serum level of liver enzymes and proteins in the control group and model group rats

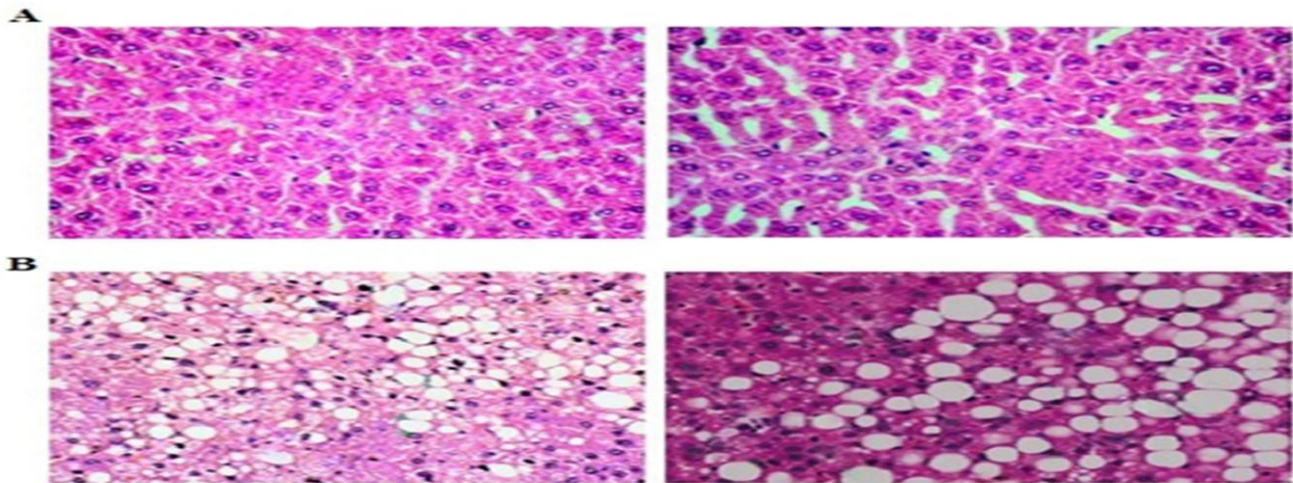
	Control group	Model group	Normal range
AST (U/L)	29.6 $\pm$ 2.30	87.6 $\pm$ 3.36	0-37
ALT (U/L)	26 $\pm$ 2.91	77.6 $\pm$ 1.52	0 – 41
Alb (g/dL)	4.22 $\pm$ 0.44	2.38 $\pm$ 0.81	2-5
TB (mg/dL)	0.78 $\pm$ 0.04	4.3 $\pm$ 0.20	1 - 0
TP (g/dL)	6.78 $\pm$ 0.49	5.52 $\pm$ 0.33	6-8
ALP (IU/L)	180.8 $\pm$ 8.64	316.2 $\pm$ 12.62	8-306

AST (aspartate aminotransferase), ALT (alanine aminotransferase), Alb (albumin), TB (total bilirubin), TP (total protein), ALP (alkaline phosphatase)

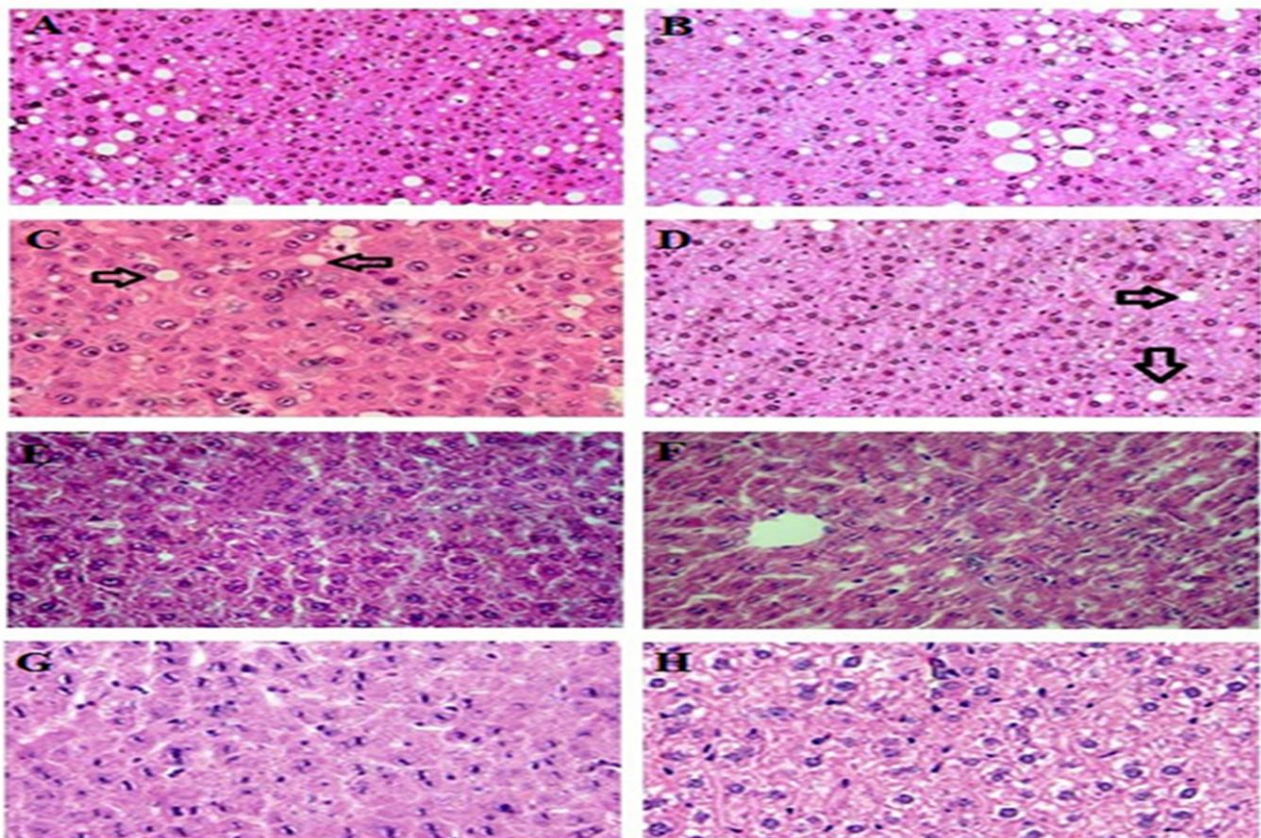
**Table 3.** Serum level of liver enzymes and proteins in the test groups rats treated by extract

	Test groups treated by different amount of burdock-chicory extract				Control	Model
	125(mL/kg)	250(mL/kg)	500(mL/kg)	1000(mL/kg)		
AST (U/L)	46.4 $\pm$ 2.61	39.2 $\pm$ 1.48	27.6 $\pm$ 2.07	29.6 $\pm$ 1.52	29.6 $\pm$ 2.30	87.6 $\pm$ 3.36
ALT (U/L)	45.6 $\pm$ 1.67	42 $\pm$ 0.71	25.4 $\pm$ 3.05	26.6 $\pm$ 1.52	26 $\pm$ 2.91	77.6 $\pm$ 1.52
Alb (g/dL)	3.78 $\pm$ 0.40	4.02 $\pm$ 0.20	4.76 $\pm$ 0.50	4.92 $\pm$ 0.23	4.22 $\pm$ 0.44	2.38 $\pm$ 0.81
TB (mg/dL)	2.4 $\pm$ 0.47	1.32 $\pm$ 0.22	0.74 $\pm$ 0.09	0.74 $\pm$ 0.05	0.78 $\pm$ 0.04	4.3 $\pm$ 0.20
TP (g/dL)	5.82 $\pm$ 0.43	6.48 $\pm$ 0.15	7.06 $\pm$ 0.19	7.24 $\pm$ 0.15	6.78 $\pm$ 0.49	5.52 $\pm$ 0.33
ALP (IU/L)	316.4 $\pm$ 11.54	273.6 $\pm$ 11.01	186.2 $\pm$ 9.42	184 $\pm$ 5.52	180.8 $\pm$ 8.64	316.2 $\pm$ 12.62

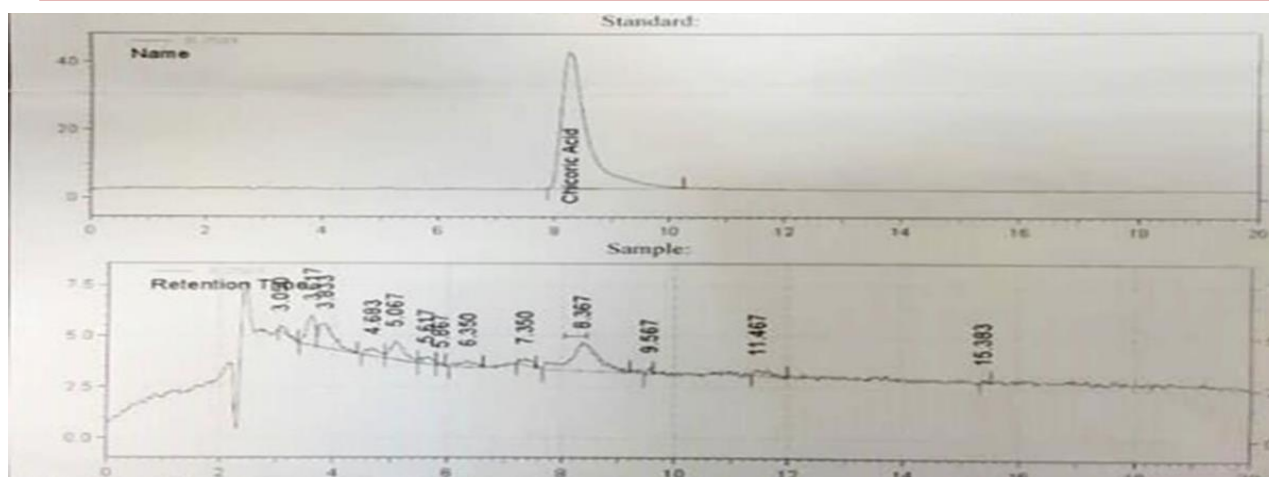




**Figure 1.** Liver histological cross-sections from the control group (A) and model group rats (B). The livers photomicrographs of the control group rats fed with normal diet showed the hepatocytes and the structure of the liver tissue remained normal (A) whereas high-fatty diet led to lipid accumulation and formation of macro-vesicular steatosis (white hollow bubbles) in livers of model group rats (B), showing that fatty liver model was successful.



**Figure 2.** Liver tissue pathology of test groups rats treated by burdock-chicory extract. A, B; the rats treated with 125 mL/kg of extract. The area of hepatic steatosis in this group decreased slightly when compared with that in the model group (Figure 1B) and lipid macro-vesicles were observable. C, D; the rats treated with 250 mL/kg of extract. The area of hepatic steatosis in this group decreased in comparison to model group (Figure 1B) and only lipid micro-vesicles (tip of arrows) were sporadically visible. E, F; the rats treated with 500 mL/kg of extract. Hepatocytes and the structure of the liver tissue were normal in this group comparing to the control group (Figure 1A), and there were no changes or necrosis in the liver cells. G, H; the rats treated with 1000 mL/kg of extract. Hepatocytes and the structure of the liver tissue were normal in this group comparing to the control group (Figure 1A), and there were no changes or necrosis in the liver cells.



**Figure 3.** Standardization of the extracts on the chicoric acid as the main active compound by HPLC. A; Chicoric acid as the standard. B; Chicoric acid presented in the aqueous extracts of burdock and chicory mixture.

## Discussion

Research has shown that fat-rich diet can lead to liver steatosis (22). Triglyceride and cholesterol are important biological lipids which excessive intake of them from food leads to hypertriglyceridemia and hypercholesterolemia (23, 24). Non-alcoholic fatty liver is characterized by the accumulation of triglycerides in the liver cells formed by the esterification of free fatty acids and glycerol. Increased free fatty acids in the liver originate from three separate sources, lipolysis (hydrolysis of triglycerides into glycerol and free fatty acids) in adipose tissue, high fat diet, and de novo lipogenesis (fatty acid biosynthesis). In contrast, fatty acids may be consumed via beta-oxidation, re-esterification into triglycerides, and storage as lipid droplets or secretion as VLDL (Very Low Density Lipoprotein).

Therefore, lipid accumulation in the liver can occur through increased de novo lipogenesis, decreased beta-oxidation or decreased lipid export as VLDL particles. Donnelly et al. (25) have shown that 60% of liver triglycerides are derived from plasma free fatty acid derived from adipose tissue lipolysis, 26% from de novo lipogenesis and another 15% from dietary fat. Increasing of liver index enzymes including AST, ALP and ALT in serum is the indicator of liver injury (26). In this study we evaluated the therapeutic effects of hydro-alcoholic extract of burdock and chicory

on fatty liver in rats fed with high fat diet and serum levels of these enzymes were assayed in the present study since the change in serum levels of these markers in liver steatosis has been reported in the previous studies (27, 28). Results showed an increase in levels of ALT, AST, and ALP enzymes in the serum of rats fed with high-fat diet which indicates damage to the liver cells. This finding is consistent with the results of Chidambaram et al. in 2010 (26). Treatment with aqueous extract of burdock-chicory prevents the elevation of serum levels of these enzymes caused by high-fat diet. In this study, the biochemical results were confirmed by histopathologic findings. The model rats fed by high-fat diet for 4 weeks showed high rates of liver steatosis while histopathologic evaluations showed the anti-hepatosteatosis effects of aqueous extract of burdock-chicory in test rats fed by high-fat diet. Park and his colleagues also investigated burdock extract in combination with three herb mixtures including *Glycyrrhiza uralensis* (licorice), *Magnolia officinalis* (magnolia), and *Zingiber officinale* (ginger) as an effective natural agent for nonalcoholic fatty liver disease and observed the herb formula inhibit lipid accumulation in hepatocytes by suppressing lipogenesis and uptake of free fatty acids (8). In another study, Al-Wabel and his colleagues investigated biological effects of aqueous extracts of six medicinal plants including burdock, chicory, fenugreek, goat's rue, colocynth and lupine mixed with stirred yoghurt filtrate against alloxan-induced oxidative stress



and diabetes in rats. Data of their research showed that the activities of the liver enzymes (AST and ALT) were decreased in sera of treated rat fed on aqueous extract of medicinal plants and stirred yoghurt filtrate mixture (29). These studies potentiate the efficiency of burdock-chicory extract in treatment of fatty liver.

## Conclusion

In conclusion, our study shows that extract of burdock-chicory has the potential to ameliorate fatty liver in rats fed with high-fat diet. This study provides evidence that burdock-chicory extract could be considered as a potential dietary supplement strategy for prevention and treatment of fatty liver.

## Acknowledgement

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## Conflict of interest

The authors declare that they have no conflict of interest.

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