

The effects of *Cynara cornigera* head extract on hyperlipidemia rat models

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Abstract: *Cynara cornigera* (CC), a member of the Asteraceae family, is widely distributed in northeastern Libya. The plant heads and leaves are traditionally used in folk medicine to manage conditions such as diabetes, hepatic dysfunction, and hyperlipidemia. The aim of this study is to investigate the effects of CC head alcoholic extract in hyperlipidemia rat models. Phytochemical screening was performed using qualitative methods. To evaluate the hypolipidemic activity, acute and sub-acute effects of CC extract (15.0% and 30.0%) were assessed in experimental rat models. The sub-acute effect of 15.0% CC extract was evaluated in diet-induced hypercholesterolemic rats fed a CCT diet (1.0% cholic acid, 4.0% cholesterol, and 0.5% thiouracil) for two weeks. Blood samples were collected to measure serum cholesterol, triglycerides, and liver enzymes, aspartate aminotransferase and alanine aminotransferase. Histopathological examination was also conducted. The phytochemical screening showed the presence of flavonoids, phenolic components, carbohydrates, tannins, and saponins. The administration of 15.0% CC showed a significant decrease in cholesterol and triglyceride levels in the protective and treatment groups. Moreover, the liver enzymes were significantly restored to normal levels in the protective and the treatment groups. In addition, the administration of CC 15.0% illustrated a normal structure and preserved parenchymal organization in the protective and the treatment groups compared with the hypercholesterolemia-induced diet. This study demonstrated that the edible CC heads ethanolic extract may have components that possess anti-hyperlipidemia activity. CC extract may prevent and protect the body from hyperlipidemia complications. Thus, the employment of such a herbal plant in conventional therapy programs may improve lipid profile.

Introduction

Medicinal plants have been used as remedies for various illnesses [1]. The use of medicinal plants is becoming increasingly widespread all over the world as an alternative treatment for various diseases. According to reports from the International Center of Commerce, medicinal plants are still essential in the preparation of pharmaceutical products [2].

Artichoke is a native plant widely spread in the Mediterranean basin. It was appreciated by the ancient Egyptians, Greeks, and Romans, who used it as food and medicine [3]. Arabs played a positive role in the dispersion of artichoke. Hence, Al harsshof was the original Arabic name of this plant, whereas it was called in Italian, Spanish, and Portuguese (Carciofo, Alcachofa, and Alcachofra, respectively), all of which were taken from Arabic [4]. In addition, The Artichoke (*Cynara*) has many species that are globally classified into different genera; some of them are well reported, such as *Cynara scolymus* and *Cynara cardunculus*, while others are not, such as *Cynara Cornigera* (CC) and the endemic plant CC [5]. In Libya, artichoke (*Cynara*) is a genus of plants that belongs to the Asteraceae family and consists of four species reported in Flora of Libya, i.e., the endemic CC, *Cynara Cardunculus*, and *Cynara Scolymus* [6]. CC is locally known as Gamool, and it is a native plant that grows wild in Mediterranean countries [7]. In folk medicine, CC (artichoke) has been used for medical and nutritional purposes. Some reports illustrated that Artichoke extracts have been utilized as cholagogues [8] to protect the liver [9] and as lipid-lowering agents [10].

Hyperlipidemia is one of the most common risk factors for the development of atherosclerosis and subsequent vascular disease, particularly increased low-density lipoproteins (LDL-hypercholesterolemia), and is simply described as elevated blood lipid or fat concentrations [11]. Worldwide, cardiovascular disease-related mortality was responsible for 14.4 million deaths globally in 1990, 17.5 million in 2005, and 20 million worldwide in 2015 [12, 13]. Moreover, the high degree of hyperlipidemia is the main risk factor for premature coronary artery disease (CAD). The incidence of CAD is associated with the highest levels of hyperlipidemia in males before the age of 55 to 60 and females before the age of 65 years. The prevalence of hyperlipidemia under the previously mentioned conditions is around 75.0% - 85.0%, compared to 40.0% - 48.0% in the control group of the same age, but without the presence of early coronary artery disease. Particularly, hypercholesterolemia-related excess LDL in the arterial wall may experience oxidative changes. The LDL cholesterol goal for every patient is based on their risk for heart and blood vessel problems, and treatment should be individualized for each patient. Primary prevention means managing risk factors, like cholesterol, to reduce the chance of getting heart and blood vessel disease [14]. Therefore, improving therapeutic options for this illness is now necessary. In this study, the effect of the CC extract on hyperlipidemia was studied in experimental animals.

Materials and methods

Chemicals for phytochemical screening tests: All the chemicals used in this study were of pharmaceutical grade and obtained from the Faculty of Pharmacy, University of Zawia, Faculty of Pharmacy, University of Tripoli, and some chemicals were obtained from laboratory chemicals at the Libyan Medical Research Center of Zawia, Libya.

Experimental animals: Male albino adult Wistar rats weighing 180 - 200 g were obtained from the animal house of the Libyan Medical Research Center, Zawia, Libya. The rats were fed a standard laboratory rat chow. Food and water were freely available ad libitum. Rats were kept in cages at 20°C - 25°C under a 12 hrs light/dark cycle.

Ethical approval: All the experiments were approved by the ethical committee of the Libyan Center of Medical Research (004-MJ-04-2026). Different concentrations of treatment were administered by oral gavage in a volume of 2.0 ml/100 g of body weight [15].

Plant collection, identification and preparation: The heads of CC were collected from Ghemines, a small town adjacent to the Gulf of Sidra in the Cyrenaica region of northeastern Libya, in March 2023. The identification of the plant was confirmed by the Department of Botany, University of Tripoli, under voucher number 685421. The heads were dried in shade and ground into a powder by a mechanical grinder. The powder was kept in stoppered amber glass bottles till the time of extraction.

Preparation of extract: The dried powder (2000 g) was macerated in 6.0 L of 96.6% ethanol for three days with continuous agitation, then filtered and concentrated by rotary evaporator at 45°C. The residue was weighed and stored in a tightly closed amber container in the fridge until use [5, 16].

Phytochemical screening: Phytochemical screening tests were performed to detect the presence of phenols, flavonoids, carbohydrates, tannins, and saponins using fresh ethanolic head extract of CC. This was carried out using the previously mentioned qualitative methods [17].

Detection of phenols by ferric chloride test: Extracts were treated with 3 - 4 drops of ferric chloride solution. Phenols are present when a blue-black color develops.

Detection of flavonoids by alkaline reagent test: Extracts were treated with a few drops of sodium hydroxide solution. When diluted acid is added, a strong yellow color forms that eventually turns colorless, indicating the presence of flavonoids.

Detection of carbohydrates by Fehling's test: Extracts were individually diluted in 5.0 mL of distilled water and then filtered. The presence of carbohydrates was examined in the filtrates. Filtrates were heated with Fehling's solution, neutralized with alkali, and hydrolyzed with dilute hydrochloric acid. Reducing sugars are present when a red precipitate forms.

Detection of tannins by gelatin test: 1.0% gelatin solution containing sodium chloride was added to the extract. White precipitate formation indicates the presence of tannins.

Detection of saponins by froth test: Diluted extracts were shaken in a graduated cylinder for 15 min after being diluted with distilled water to a volume of 20.0 mL. The presence of saponins is indicated by the formation of a 1.0 cm layer of foam.

Measurement of lipid (cholesterol and triglyceride) in normal rats:

Acute treatment of 30.0% w/v CC extract: 12 rats of either sex were divided into two groups (n = 6): Group I: Control group and received 5.0% gum acacia in distilled water. Group II (test group) received 30.0% w/v extract suspended in 5.0% w/v gum acacia. After two hours, a blood sample was collected by cardiac puncture. Serum was separated by centrifugation at 3000 rpm for five minutes; cholesterol and triglycerides were measured.

Sub-acute treatment of CC extract: 12 rats were divided into two groups (n = 6); the control group received vehicle control 5.0% w/v gum acacia in distilled water. Group II: The test group received 15.0% w/v CC extract suspended in 5.0% w/v gum acacia. Each rat was housed separately in cages; the vehicle and treatment were given once daily for a week. On day seven, all rats were killed under anesthesia, and a blood sample was collected by cardiac puncture; serum was separated by centrifugation at 3000 rpm for five minutes. Cholesterol and triglycerides were measured.

Hypercholesterolemia-inducing diet by CCT: 12 rats were used for the experiment. Hypercholesterolemia was induced by oral gavage of 4.0% cholesterol, 1.0% cholic acid, and 0.5% thiouracil (CCT diet) daily for two weeks [18, 19].

Experimental design for treatment of CC extract in diet-induced hypercholesterolemia rats: 12 rats were divided into four groups (n = 6 per group). Group I (control): Rats were given distilled water and served as the control group. Group II (Hypercholesterolemia induction), III, and IV rats were fed a CCT diet once daily for 14 days. For the protective and therapeutic effect of CC extract, the rats in Group III (protective) received CC 15.0% w/v alongside with the CCT diet for 14 days. On the other hand, Group IV (treatment) received 15.0% w/v CC for another 14 days after the CCT diet. After 24 hrs at the end of the first two weeks of the experiment, rats of Group

I and Group III were sacrificed under anesthesia (ether), and the other two Groups, II and IV, were sacrificed two weeks later; then the blood was collected by using cardiac puncture for biochemical measurements, i.e., cholesterol, triglycerides, aspartate aminotransferase (AST), and alanine transaminase (ALT). Sections of the liver were isolated after sacrifice of rats and immediately immersed in 10.0% formalin to undertake histopathological investigations.

Measurement of cholesterol and triglyceride levels: An enzymatic colorimetric method was applied in this study. The intensity of the color developed was measured spectrophotometrically against a blank at a wavelength of 520 nm [20, 21].

Measurement of AST and ALT levels: The IFCC Kinetic method was applied using the serum [22, 23].

Histopathological study: All 24 liver samples were processed at the Libyan Medical Research Center following the validated methods of tissue fixation in 10.0% formalin for 24 hrs. Washing was done in tap water, then periodic dilutions of alcohol were used for dehydration. Samples were cleared in xylene and embedded in paraffin at 56 °C in an oven for 24 hrs. Paraffin wax tissue sections were prepared for sectioning at four-micron thickness by a microtome. The tissue sections were collected on glass slides. Deparaffinized and stained with hematoxylin and eosin for examination under a light microscope. Finally, Photomicrography was performed for the samples [24].

Statistical analysis: Descriptive statistical analysis was applied to the general data from different samples using SPSS (Software package, version 26) to find out whether the observed samples are normally distributed using the Kolmogorov-Smirnov maximum deviation test for goodness of fit. If the parameters were normally distributed, treatments were compared by applying analysis of variance (one-way ANOVA), followed by post hoc tests (LSD and Duncan tests) to compare individual means. If the data were not normally distributed, the non-parametric Mann-Whitney test was applied. All data were expressed as mean $\pm$ SEM, and the differences were considered to be significant at $p < 0.05$.

Results

Phytochemical screening tests: The results of the phytochemical screening of the ethanolic heads extract of *CC* by using different chemical methods, as mentioned before, revealed that the extract contains different active constituents. **Table 1** shows the active constituents and their methods of detection. The tests were indicated positive for the presence of flavonoids, phenolic components, carbohydrates, tannins, and saponins.

Table 1: Phytochemical screening tests of *Cynara cornigera* extract

Constituents /tests	Observations	Findings
Flavonoids Alkaline tests	Colorless	+
Phenolic components: Ferric chloride test	Dark blue color	+
Carbohydrates Fehling's test	Red precipitate	+
Tannins Gelatin test	White precipitate	+
Saponins Foaming test	Formation of foam	+

+ indicates the presence of active constituents

Acute effect of CC extract on cholesterol levels: The results revealed that there was no significant effect on cholesterol levels after one dose of CC 30.0% w/v between control and treated groups (**Figure 1**).

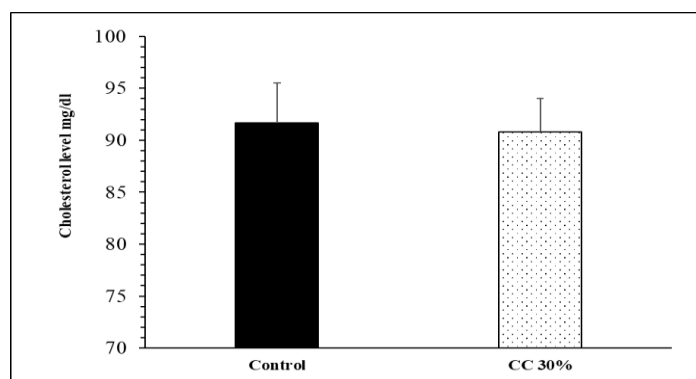


Figure 1: Acute effect of *Cynara cornigera* extract on cholesterol levels in normal rats
Cholesterol levels were expressed (mg/dl) as mean $\pm$ S.D.

Acute effect of CC extract on triglyceride levels: The results showed no significant effect on triglyceride levels after one dose of CC 30.0% w/v between the control and treated groups (**Figure 2**).

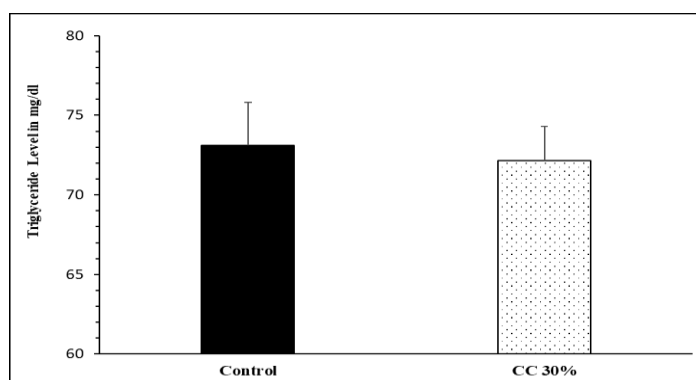


Figure 2: Acute effect of *Cynara cornigera* extract on triglyceride levels in normal rats
Triglyceride level results were expressed (mg/dl) as mean $\pm$ S.D.

Sub-acute effect of CC extract on cholesterol levels: The results revealed that there is a slight but not significant effect on cholesterol levels after one-week administration of CC 15.0% w/v between control and treated groups (**Figure 3**).

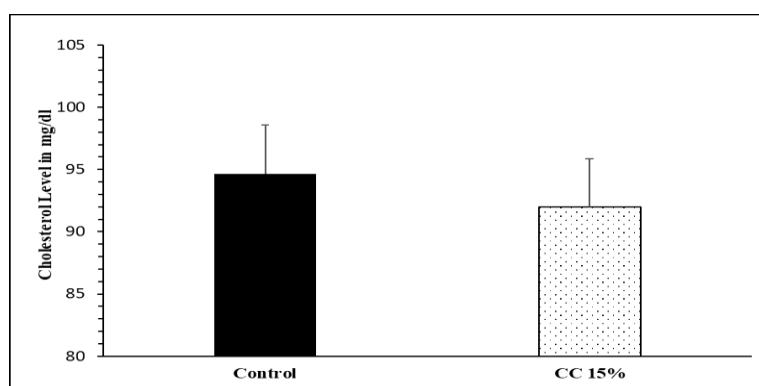


Figure 3: Sub-acute effect of *Cynara cornigera* extract on cholesterol levels in normal rats
Cholesterol level results were expressed (mg/dl) as mean $\pm$ S.D.

Sub-acute effect of CC extract on triglyceride levels: The results revealed that there was no significant effect on triglyceride levels after one-week daily administration of CC 15.0% w/v between control and treated groups (**Figure 4**).

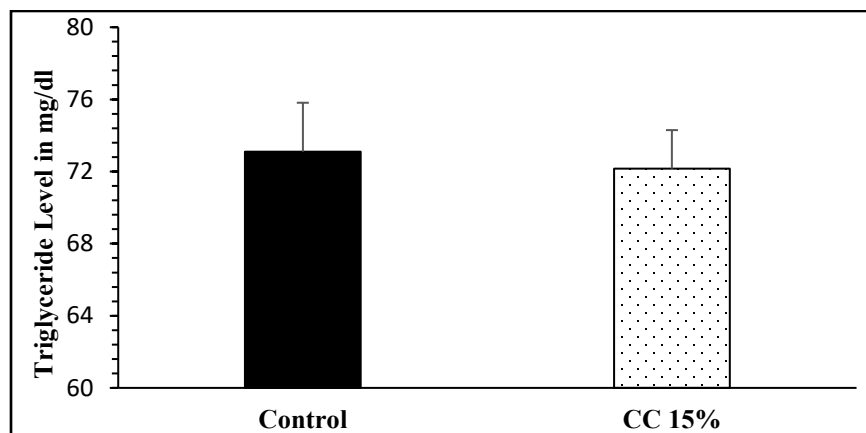


Figure 4: Sub-acute effect of *Cynara cornigera* extract on triglyceride levels in normal rats
Triglyceride levels (mg/dl) were expressed as mean $\pm$ S.D.

The effect of CC extract on cholesterol levels in the diet-induced hypercholesterolemia model: The effect of CC 15.0% w/v administration on cholesterol levels was significantly decreased ($p < 0.05$) in the treated and protective groups compared to the CCT (Cholo-diet) group. Cholesterol levels were also significantly increased in the diet induced-hypercholesterolemia group compared to the control group (**Figure 5**).

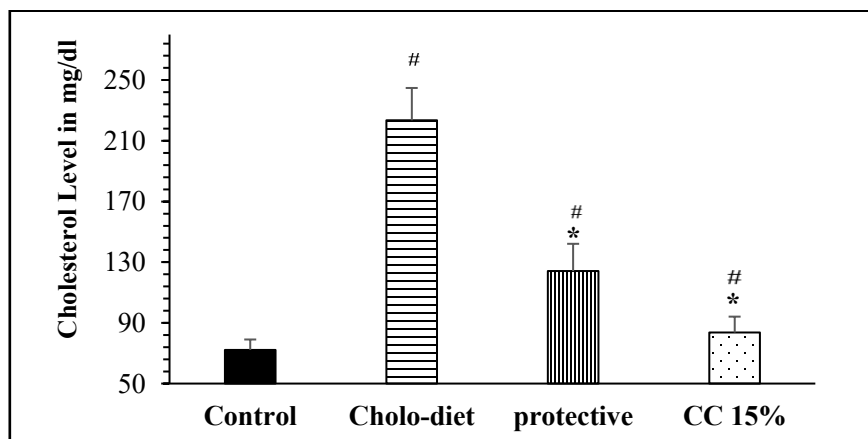


Figure 5: Effect of *Cynara cornigera* extract on cholesterol levels in hypercholesterolemia-induced diet rats
Cholesterol levels (mg/dl) were expressed as mean $\pm$ S.D.

* indicates a significant difference from cholo-diet group. # indicates a significant difference from the control group at $p < 0.05$, $n = 6$.

The effect of CC extract on triglyceride levels in the diet-induced hypercholesterolemia model: The effect of CC 15.0% w/v administration on cholesterol levels was significantly decreased ($p < 0.05$) in the treated and protective groups compared to the CCT (Cholo-diet) group. Also, cholesterol levels were significantly increased in the diet induced-hypercholesterolemia group compared to the control group (**Figure 6**).

The effect of CC extract on AST levels in the diet-induced hypercholesterolemia model: The effect of CC 15.0% w/v administration on AST levels was significantly decreased ($p < 0.05$) in the treated and protective groups compared to the CCT group. AST levels were significantly increased in the diet-induced hypercholesterolemia group compared to the control group (**Figure 7**).

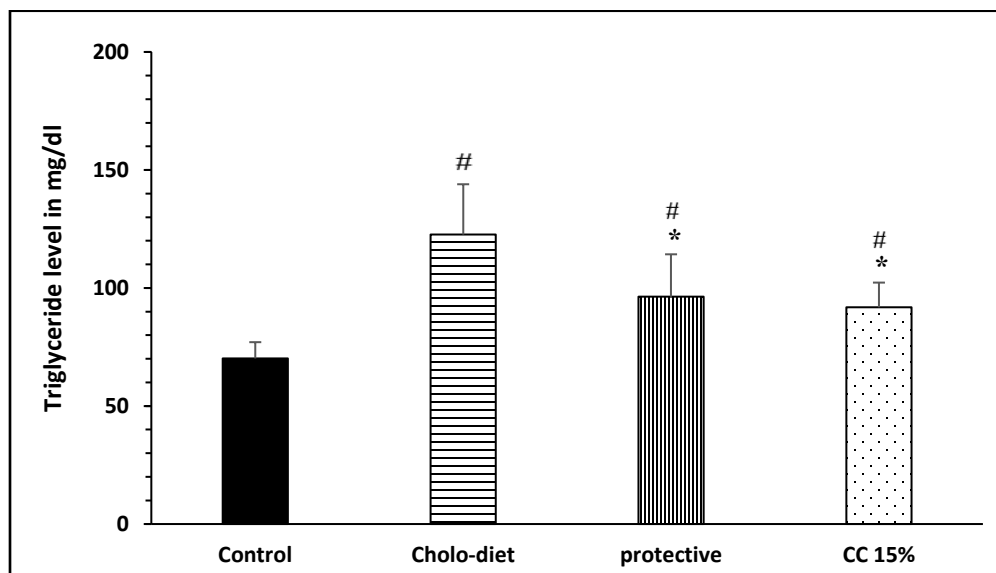


Figure 6: Effect of *Cynara cornigera* extract on triglyceride levels in diet-induced hypercholesterolemia-induced diet rats. Triglyceride levels (mg/dl) were expressed as mean $\pm$ S.D. * indicates a significant difference from the hypercholesterolemia-induced diet (Cholo-diet) group. # indicates a significant difference from the control group at $p < 0.05$, $n = 6$.

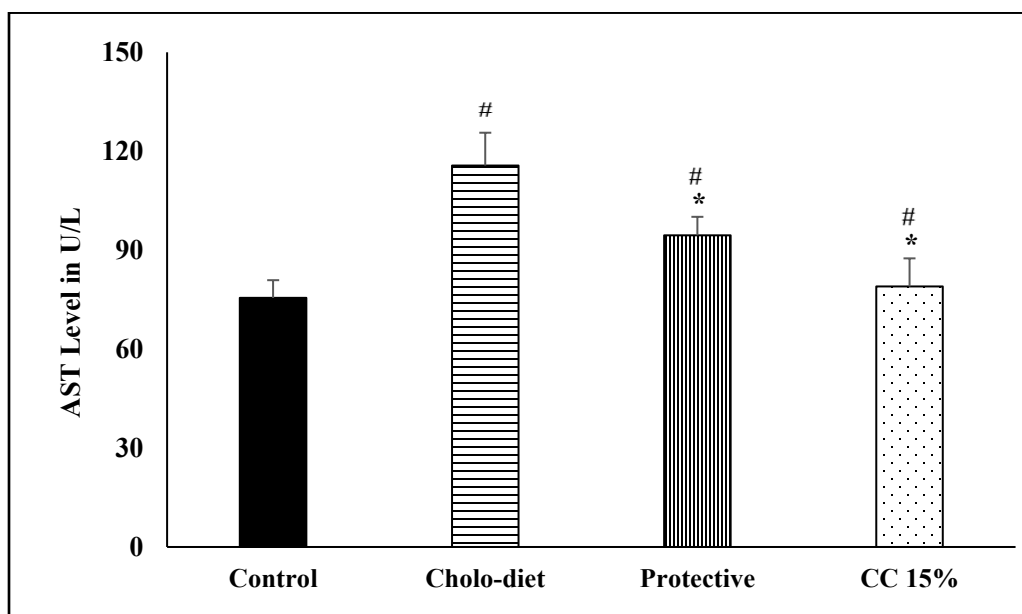


Figure 7: Effect of *Cynara cornigera* extract on AST levels in diet-induced hypercholesterolemia model:

Aspartate aminotransferase (AST) levels (U/L) were expressed as mean $\pm$ S.D. * indicates a significant difference from the diet-induced hypercholesterolemia (CCT) (Cholo-diet) group. # indicates a significant difference from the control group at $p < 0.05$, $n = 6$.

The effect of CC extract on ALT levels in the diet-induced hypercholesterolemia model: The effect of CC 15.0% w/v administration on ALT levels was significantly decreased in the treated and protective groups compared to cholo-diet group. ALT levels were significantly increased in the cholo-diet group compared to the control group (Figure 8).

Histopathological study of liver: The microscopic examination of liver tissue sections (H and E, 20x) demonstrated severe fatty changes in group II (diet-induced hypercholesterolemia) induced by the CCT diet. Whereas groups III (protective) and IV (treated), which were administered CC 15.0% w/v, illustrated a normal structure along with marginal fat cells and preserved parenchymal organization. The recovery of hepatic tissue damage restored from CCT damage after CC extract treatment (Figure 9).

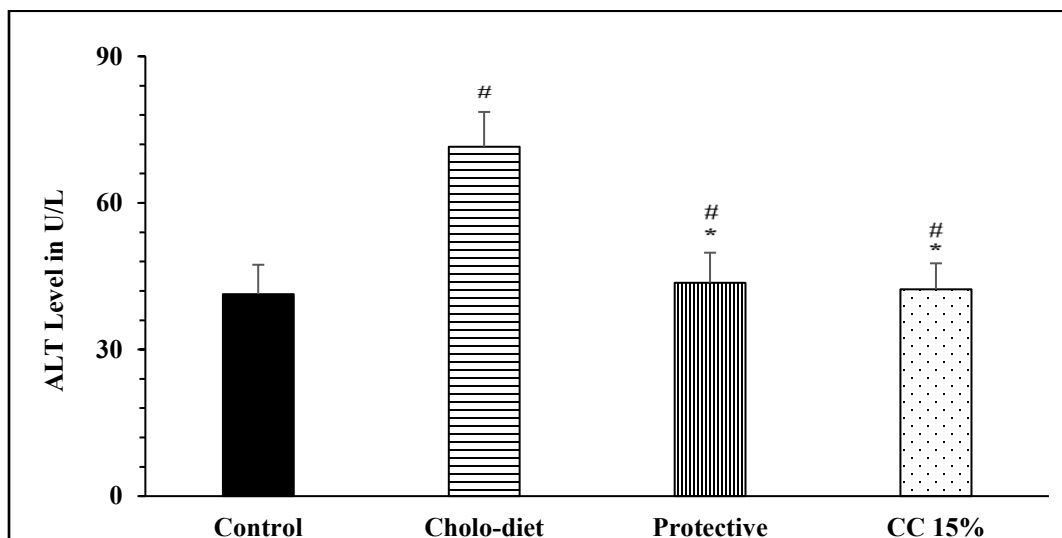


Figure 8: Effect of CC extract on ALT levels in diet-induced hypercholesterolemia model

The alanine transaminase (ALT) levels (U/L) results were expressed as mean $\pm$ S.D. * indicates a significant difference from the diet-induced hypercholesterolemia (cholo-diet) group. # indicates a significant difference from the control group at $p < 0.05$, $n = 6$.

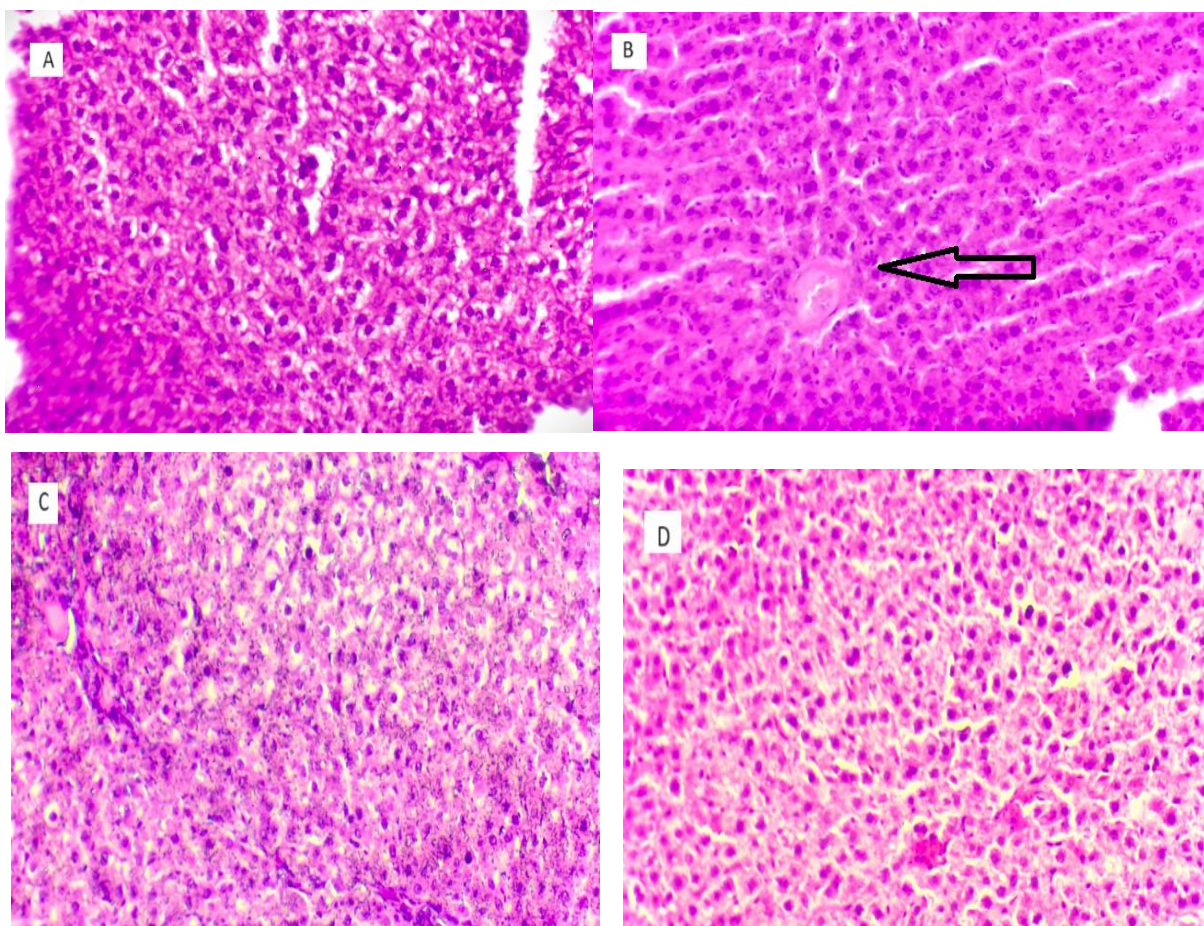


Figure 9: Effect of *Cynara Cornigera* extract on histopathology of liver rats in a diet-induced hypercholesterolemia model

Histopathology of Liver rats fed a diet-induced hypercholesterolemia diet, showing the effect of *Cynara Cornigera* 15.0% w/v extract. (A) Group with normal parenchymal liver structure in rats. (B) Group of diet-induced hypercholesterolemia (cholo- diet or CCT) fed rats, which show fatty changes in liver cells. (C) Group of co-treated (protective) *Cynara Cornigera* and diet-induced hypercholesterolemia (CCT diet) which appears to have normal hepatic cells with very occasional fat cells, as in the (D) group (H & E 20x).

Discussion

Medicinal plants have an essential role in human medicine preparations for preventive and curative purposes [25]. Many plant species have therapeutic characteristics, which have helped traditional medicine to spread widely in various nations [26]. Artichokes are very common in the Mediterranean region and have been utilized in traditional medicine since ancient times due to their known therapeutic benefits [27]. Many studies have illustrated that there is a relationship between the therapeutic use and chemical components that have biological benefits.

In this study, the phytochemical tests of *CC head* extract confirmed the presence of flavonoids, phenolic components, carbohydrates, tannins, and saponins, which were found to be consistent with previous studies on other species of artichoke. In Libya, *CC* is not well studied. These active components may be responsible for the traditional use of this plant to treat different illnesses, such as antioxidant, antibacterial, anti-hyperlipidemia, and anti-hyperglycemia [27-29]. Some reports illustrated indirectly that *CC* extract showed notable beneficial effects in reducing hyperlipidemia parameters [5]. Therefore, this encourages us to pursue further studies to investigate the anti-hyperlipidemic activity of *CC* in a proper model of hyperlipidemia, which is diet-induced hypercholesterolemia. This type of diet is a rat chow supplemented with 1.0% cholic acid, 4.0% cholesterol powder, and 0.5% Thiouracil (CCT) [18]. This method was validated to increase plasma cholesterol and triglyceride levels [19, 30-32]. The significant elevation of blood cholesterol levels could be due to the indirect effect of thiouracil on cholesterol metabolism [33], where the anti-thyroid property increases the serum cholesterol level by enhancing the release of circulating thyroid hormones [34], as well as the cholic acid administration that enhances the absorption of cholesterol [35]. As can be concluded from **Figures 5 and 6**, the administration of the extract lowered the cholesterol and triglyceride levels in the treated and protective groups. Thus, these results agree with the effect of other species of artichoke that have a hypolipidemic effect [35, 36], which is properly due to the presence of the flavonoid component luteolin [27]. Other studies indicate that luteolin is essential in *CC* ability to prevent cholesterol synthesis [10].

Furthermore, the mechanism of cholesterol inhibition could be by inhibiting the activity of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which is the key enzyme of cholesterol biosynthesis [38]. The *CC* extract's inhibitory effect on hydroxymethylglutaryl-CoA (HMG-CoA) reductase is explained in **Figure 10**. This effect most likely results from other interactions, indirectly through the activation of inhibitory mechanisms or the inhibition of activating processes. As a result, *CC* seems to prevent the production of lipids on many different levels. Thus, it was unexpected that plant extract would accumulate the undesirable sterol compounds noticed for certain synthetic lipid-lowering drugs [38, 39]. In fact, these results revealed that the anti-hyperlipidemic effects of luteolin glycosides and caffeoylquinic acids were both thought to be responsible [27, 29, 40].

Luteolin was also believed to be one of the artichoke components that blocked the *Novo* cholesterol synthesis [41]. Thus, this effect could be the reason for the significant protective effect of *CC* extract on hyperlipidemia (**Figure 5**). It can be concluded that the bioactive compounds in *CC* extract were responsible for the lipid-lowering parameters, total cholesterol, and triglyceride levels in the treatment and protective groups in this study. This is in line with previous studies [10, 27]. However, more research is needed to understand the exact mechanism of *CC* extract on lipid profile and its protective properties against hyperlipidemia. CCT also has an impact on the animal's liver, producing damage and an increase in weight. These changes are most likely based on the liver's greater fat content [42-46]. Also, several studies have linked a high dietary fatty acid intake to liver injury [47-49]. Studies demonstrated that liver damage was clearly indicated by the elevation of hepatic marker enzymes AST and ALT in the hypercholesteremic diet groups [50, 51]. Moreover, other reports demonstrated that the CCT diet causes liver damage through the generation of adenosine, alkaline phosphatase, and interleukin-6 [52].

In the current study, *CC* extract has a significant effect on liver marker enzymes AST and ALT, by their restoration to normal levels in the treated group and nearly normal levels in the protective group (**Figures 7 and 8**). These results are in agreement with findings from other species of artichoke, as they were found to reduce rats' liver enzymes [9, 29, 41]. The effect of the *CC* extract may be contributed to by active compounds such as caffeoylquinic acid, chlorogenic acid, cynaroside, and scolymoside that have been approved to have a hepatoprotective effect [28, 29]. However, this effect may be due to the consideration of Artichokes as an ideal remedy to assist in achieving optimal liver function because they prevent the process of lipid peroxidation from developing in the cell membranes of the liver's tissues, which helps to eliminate harmful toxins and digest fats through the liver's generation of bile [53-55]. Another explanation it is may be contributed to the elevation in bile acid flow by increasing the bile acid concentration that would rise the cholesterol elimination which have been reported in artichoke leaf extract research [56-58]. Previous investigations have shown a hepatoprotective effect associated with antioxidants on rat hepatocytes, cultured endothelial cells, monocytes, and an *in vivo* rat model [9, 59, 60]. Furthermore, other studies showed additional antioxidant capabilities by inhibiting LDL oxidation [61]. ALE (Artichoke Leaf Extract) is well-known as an antioxidant. Thus, numerous *in vitro* investigations have shown that this activity is caused by the metal ion chelating and radical scavenging properties of ALE's components, including cynarin, flavonoids, and chlorogenic acid [61-63]. Interestingly, the above-mentioned findings are in agreement with the histopathology investigation of this study, as the effect of *CC* extract on the liver sections provided a defense against the harmful parenchymal modifications in the hepatic tissue caused by the CCT diet. However, the exact effect of *CC* extract is still unknown, and further investigations are needed to prove the exact mechanism of such a plant.

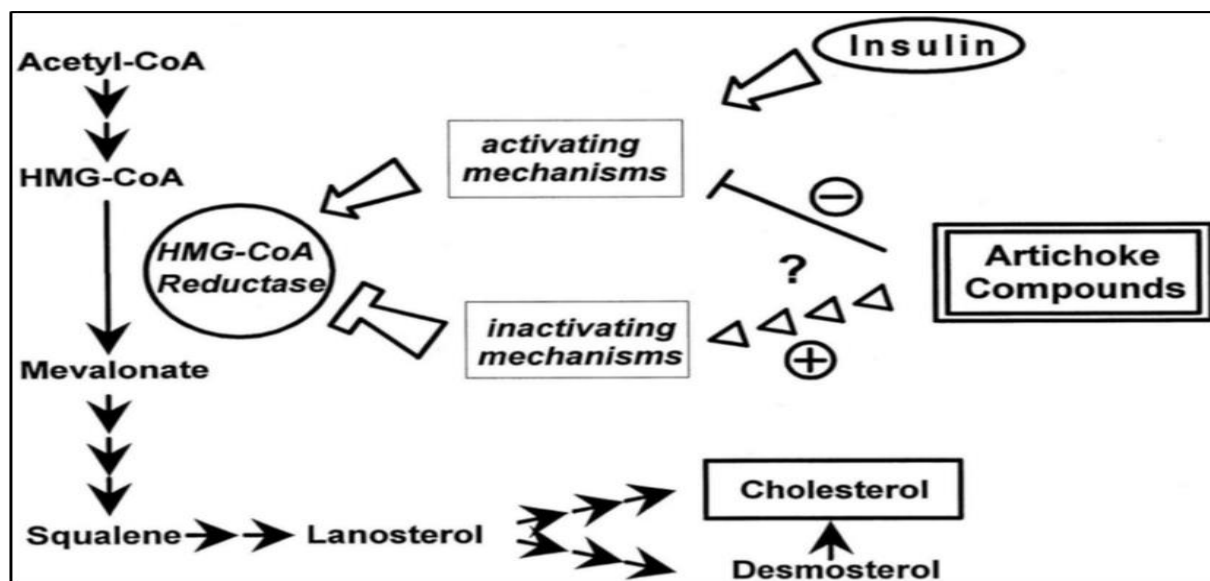


Figure 10: Effect of Artichoke components on cholesterol biosynthesis: Shows the explanation of the cholesterol biosynthesis pathway using a schematic presented to show how artichoke compounds could work.

The diagram provides a condensed summary of the enzymatic processes involved in the production of cholesterol from Acetyl-CoA. As stated, artichoke components may indirectly lower the activity of HMG-CoA reductase by inhibiting regulatory mechanisms that activate the enzyme and/or stimulating regulatory mechanisms that deactivate it [10].

Conclusion: This study demonstrated that the edible *Cynara Cornigera* heads ethanolic extract may consist of components that possess the ability to decrease hyperlipidemia. Moreover, *Cynara Cornigera* extract may prevent and protect the body from hyperlipidemia. Thus, the employment of such herbal plants in conventional therapy programs may improve lipid profile.

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