Antidyslipidemic Effects and Improvement in Lecithin–Cholesterol Acyltransferase (LCAT) Activity Following Dietary Supplementation with a Mixture of *Olea europaea* and *Cynara scolymus* Leaves in a Rat Model

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ABSTRACT

Background: *Olea europaea* (OeP) and *Cynara scolymus* (CsP) are commonly found in the Mediterranean region, including Algeria, and have traditionally been used to treat various ailments, including dyslipidemia.

Aim: To explore the activity of lecithin-cholesterol acyltransferase (LCAT) in OeP and CsP leaves using a hypercholesterolemia diet-induced dyslipidemia model in rats.

Materials and Methods: To develop the dyslipidemia animal model, 21 adult Wistar rats were chosen and fed a hypercholesterolemia diet (2% cholesterol and 1% cholic acid) for up to 15 days. Dyslipidemia was confirmed in the rats through biochemical tests. Subsequently, the rats were given a diet enriched with couscous and Oep and Csp leaves powder supplements (1%) for 15 days of consecutive treatment. Under sodium pentobarbital anesthesia, blood samples were collected and stored at -70°C for biochemical analysis.

Results: The study revealed that the Oep and Csp leaves treated dyslipidemia rats significantly ($p<0.01$) decreased FSG, TC, FC, TG, phospholipids, LDL-c, ApoB-100, creatinine, urea, AST and ALT. By contrast, other biochemical parameters, including HDL-C, LCAT, and ApoA-I, were significantly ($p<0.01$) improved compared to the dyslipidemia control rats.

Conclusion: Current investigation concludes that OeP and CsP leaves exhibit lipid-lowering and anti-dyslipidemia effects by enhancing LCAT activity in hypercholesterolemia-induced dyslipidemia model rats.

Keywords: Dyslipidemia; Olea europaea; Cynara scolymus; Lecithin-cholesterol acyltransferase; Lipoprotein.

INTRODUCTION

Dyslipidemia is a chronic, metabolic condition characterized by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C) **[1].** In dyslipidemia, cardiovascular diseases (CVDs) are a major independent risk factor, leading to high mortality, disability, and medical expenses globally. In addition, Dyslipidemia is a major risk factor for atherosclerosis, thrombosis, coronary heart disease, and ischemic stroke. Researchers assert that high non-high-density lipoprotein cholesterol is the

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primary cause of ischemic heart disease and stroke, resulting in approximately 3.9 million deaths globally. Since primary prevention is crucial in reducing the incidence of CVDs, advancements in managing dyslipidemia are instrumental in decreasing the morbidity and mortality associated with these conditions **[2].** To determine the primary cause of dyslipidemia, researchers suggest that the nature of work, less physical activity, unhealthy diets, and the working environment may be linked to dyslipidemia **[3].**

The prevalence of dyslipidemia has increased over the last three decades and is considered a health burden globally. An increased prevalence of dyslipidemia in young adulthood is a concern as it increases the risk of coronary heart disease in later life. In addition, it has been suggested that about 50% of young adults with elevated total cholesterol have five times the risk of coronary heart disease and nine times the risk of myocardial infarction than those having low total cholesterol levels over 30 to 40 years of age **[3].** The WHO reports that 39% of the adult population globally is affected by high blood cholesterol levels. Furthermore, CVDs result in approximately 12 million deaths each year worldwide. In Algeria, about 51% of the total population suffers from dyslipidemia and its complications related to CVDs **[4-5].**

Various conventional drugs have been used to mitigate dyslipidemia and its associated complications; however, most of them have some drawbacks. Statins are such kind of drugs to lower lipid levels but they can lead to adverse reactions such as muscle pain, liver damage, and diabetes, especially when taken in high doses. Fibrates, another type of medication for dyslipidemia, also have some side effects reported like muscle problems, elevated liver enzymes, and gallstones. Moreover, some patients do not respond well to this medication and may develop resistance. Therefore, there is a crucial necessity for the development of new and alternative therapies for dyslipidemia **[6-7].**

Since ancient times, plants and their derivatives have been used to treat a variety of illnesses all over the world because of their low risk of negative side effects and affordability **[8]**. *Olea europaea* and *Cynara scolymus* are two plants found globally, including in Algeria. Different parts of Olive tree (*O europaea)* and artichoke (*C scolymus)* have been used to treat various conditions, including anti-inflammatory, antioxidant, liver-protective, bile-expelling, antimicrobial, lipid-lowering, neuroprotective, CVDs, hypertension, neurological metabolic, and cancer-related diseases **[9-11].** Researchers have revealed that *O europaea* and *C scolymus* leaves are abundant sources of antioxidants and phytocompounds such as alkaloids, cardiac glycosides, flavones, flavonoids, steroids, tannins, terpenoids **[12-13].** The phenolic-rich extract of *O europaea* leaves has been reported to have antihyperlipidemic, antidiabetic, anticholesterolemic, and antidyslipidemic activities. Moreover, *C scolymus* leaves extracts have been reported to reduce plasma lipid levels, including total cholesterol **[14-15].** Therefore, the current study was designed to evaluate the effects of a combination of *O europaea* and *C scolymus* leaves on improving Lecithin-Cholesterol Acyltransferase Activity (LCAT) against dyslipidemia in cholesterol-rich diet-fed on Wistar rats.

MATERIALS AND METHODS

Plant materials

In September 2023, leaves of *O europaea* (olive) and *C scolymus* (artichoke) were collected from a suitable area in Algeria. The collected samples were washed with tap water and air-dried for a week. After drying, the samples were ground using a grinder machine, and the resulting fine powder was stored in hermetically sealed glass containers for future use.

Preparation of enriched couscous of *O europaea* and *C scolymus* leaves

Traditional artisanal couscous was made from semolina and blended with 1% powder of *O europaea* and *C scolymus* leaves. The couscous was hydrated, rolled, and sieved. It was then pre-cooked (vaporized) and placed in

an area away from light until it was completely dry.

***In vivo* study**

Before the *in vivo* study, the sample size was calculated using the following equation:

Sample size = $[2 \times (SD)^2 \times (Z(\alpha/2) + Z(\beta))^2] / d^2$

The sample size consisted of 7 animals per group, and the experiment was carried out with three different groups: a Normal Control (NC), a Dyslipidemia Control (DC), and a group supplemented with OeP and CsP leaves powder. This results in a total of 21 animals. **[16].** Three-month-old adult 21 male Wistar rats were collected from the animal facility of the University of Mascara, Mustapha Stumbouli, Mascara, Algeria, where rodents were kept by maintaining animal husbandry stable temperature (22-23°C) and humidity (60%), with a 12-hour light-dark cycle and animal ethics guidelines. In addition, the study was approved by the institutional animal research committee.

Animal model preparation

Adult Wistar rats (150 ± 5 g), were fed a freshly prepared diet that included 2% cholesterol and 1% cholic acid (Sigma-Aldrich, Germany) in addition to their standard diet for 15 days. The ingredients for the standard feed water, Crude protein, Crude fat, Carbohydrates, Ash, and minerals (Ca+, P, Na, Fe) were mixed in the following standard proportions (Table 1). The feed, supplemented daily with 2% cholesterol and 1% cholic acid, was prepared fresh each day throughout the experimental period, lasting up to 15 days. After a cholesterol-enriched diet, dyslipidemia in the rats was confirmed by assessing their fasting lipid profiles and monitoring their body weights **[17].** Afterward, rats confirmed with dyslipidemia were given a diet consisting of cholesterol (2%) and cholic acid (1%) for 15 days, mixed with OeP and CsP (1%) in the supplemented groups (Table 1). In contrast, the NC group was fed a normal balanced diet, while the DC group continued on the cholesterol diet throughout the experiment. Body weight was measured weekly, and in the final week of the experiment, the rats were placed in metabolism cages to collect their urine and feces.

Table 1: Diet chart for preparing dyslipidemia animal model (n=7)

Ingredients (%)	NC (n=7)	DC (n=7)	OeP and CsP sup
Water	13	13	13
Crude protein	12.5	12.5	12.5
Crude fat	2.5	2.5	2.5
Carbohydrates	75	75	75
Ash	1.7	1.7	1.7
Ca+	0.35	0.35	0.35
P	36.9	36.9	36.9
Na	0.05	0.05	0.05
Fe	0.45	0.45	0.45
Cholic Acid	-	1	1
Cholesterol	-	2	2
*Oe*P	-	-	1
*Cs*P	-	-	1

NC: Normal Control; DC: dyslipidemia control; OeP and CsP sup; OeP : Olea europaea leaves powder ; CsP : Cynara scolymus leaves powder supplement.

Blood and organ collection

During animal model preparation fasting (12hrs); lipid profile analysis blood samples were collected from the rats through the caudal vein. At the end of the study, blood was collected by pucture of the abdominal aorta. Rats were anesthetized by intraperitoneal injection of sodium pentobarbital (60 mg/kg bw). Afterward, blood was centrifuged and the serum & the pellet containing erythrocytes were separated from the collection tubes. In addition, the liver was carefully removed, rinsed with NaCl physiological solution (0.9%), dried, and weighed. All the serums and organs were stored at -70°C for further biochemical analysis.

Estimation of total lipids from liver and feces

By following the method of Delsal. 1944, total hepatic and fecal lipids were determined [18].

The total lipid percentage in the sample was calculated by subtracting the initial weight of the empty flask from the final weight of the flask containing the lipid extract.

Determination of total and free cholesterol, cholesterol esters, HDL-c and LDL-c

Fecal, serum, and liver total cholesterol (TC) and free cholesterol (FC) concentrations were quantified using the enzymatic colorimetric method (CHOD-POD Sprinreact, Spain; Biolabo, France) at a wavelength of 500 nm **[19].**

Determination of triglyceride, phospholipid, apolipoprotein A-I and B-100

Triglycerides and phospholipids (PL) were determined in serum and liver using colorimetric enzymatic methods (GPO-POD Sprinreact Spain; Cypress Diagnostics, Belgium) [20]. Serum apolipoproteins A-I and B-100 were determined by turbidimetric method (Spinreact, Spain) [21].

Enzyme activity of LCAT

Endogenous LCAT activity was determined using the technique of Albers et al. 1986 on fresh serum [22]. This technique is based on the disappearance of FC, which is transformed into esterified cholesterol (EC) from a fatty acid and lecithin under the action of LCAT, after 4 h incubation at 37°C. FC was determined by a colorimetric enzymatic method (Biolabo, France).

Biomarkers of liver and kidney function

Serum levels of glucose (Spinreact, Spain), uric acid (Spinreact, Spain), urea (Chronolab, System), creatinine (Biocon, Germany), transaminases (Chronolab, System) and albumin (Biolabo, France) were determined by enzymatic colorimetric techniques.

Statistical analysis

All the results were expressed as mean ± standard deviation (M±SD) and the comparison of means was performed by student t-test (P< 0. 01).

RESULTS

Determination of body weight, consumed food, hepatic & fecal total lipids in dyslipidemia rats

Table 2 compares the different treated group rats' body weight, food intake, and fecal and hepatic total lipids. The study revealed that the OeP and CsP -supplemented group had a 1.4% decrease in body weight and a 3% decrease in food intake compared to the DC group. There were no significant differences in consumed food and body weight. However, fecal lipids were significantly ($p<0.01$) increased while hepatic total lipids were significantly ($p<0.01$) reduced when compared to the DC-treated rats, respectively.

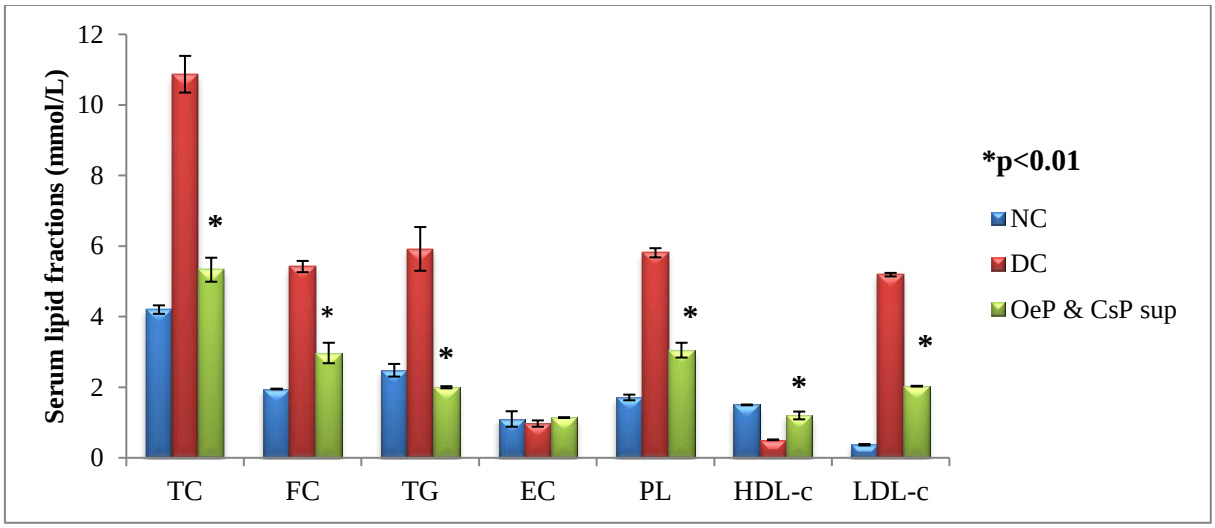
Table 2: Body weight, food consumed, fecal and hepatic total lipid levels. (M±SD).

Parameters	NC (n=7)	DC (n=7)	OeP and CsP sup (n=7)
Body weight (g)	197.05±18.26	230.47±8.54	227.03±5.77 (1.4%↓)
Food consumed (g/day /rat)	22.20±1.50	25.00±2.03	24.34±1.64 (3%↓)
Fecal total lipids (mg/day/ rat)	55.03±3.12	40.62±5.17	61.00±0.91* (50%↑)
Hepatic total lipids (mg/g liver)	10.11±0.02	23.07±1.43	19.41±1.08* (16%↓)

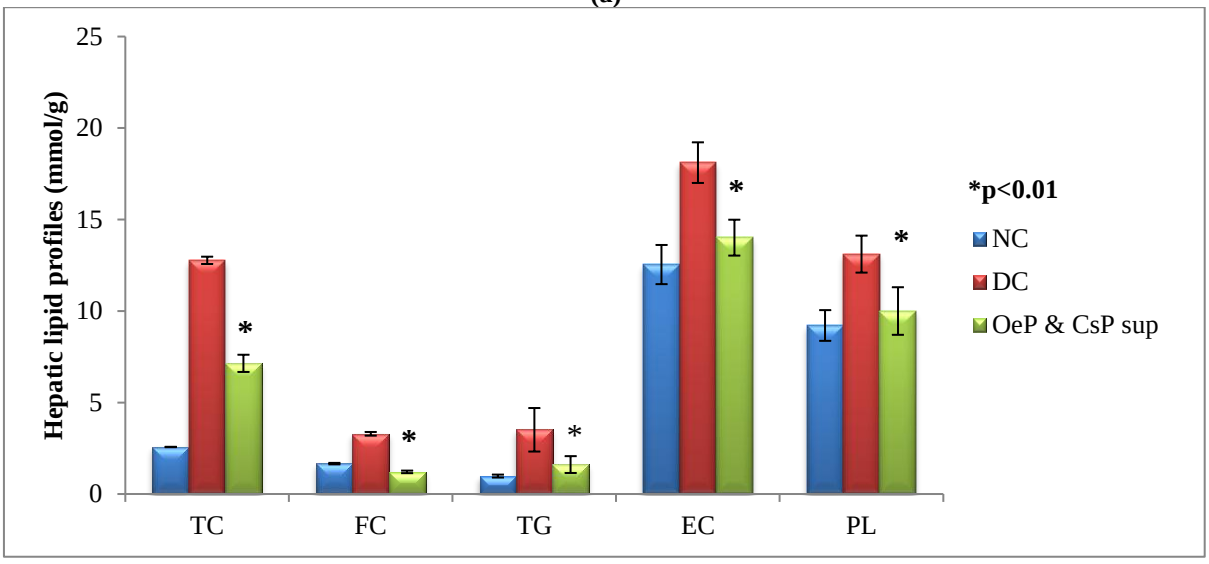
NC: Normal Control ; DC: dyslipidemia control ; OeP and CsP sup ; *Oe*P : *Olea europaea* leaves powder ; *Cs*P : *Cynara scolymus* leaves powder supplement.*p<0.01.

Evaluation of fasting serum, liver and fecal lipid fractions on OeP and CsP sup treated dyslipidemia rats.

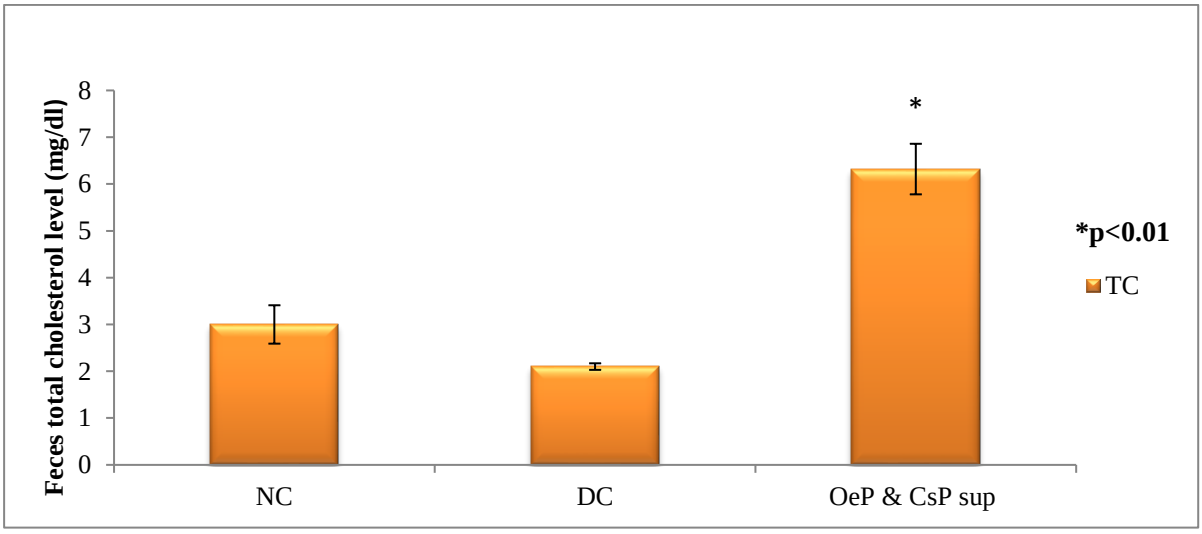
Figure 1 (a, b, c) shows the results for the OeP and CsP-supplemented treated group of rats compared to the control groups. The fasting serum, liver, and fecal lipid fractions were analyzed. Treatment with OeP and CsP-supplemented significantly reduced fasting serum TC, FC, TG, PL, and LDL-c, all with a significant level of $p < 0.01$. At the same time, HDL-c levels were significantly increased ($p < 0.01$). However, EC slightly increased in the OeP and CsP sup-treated rats (Figure 1a). The liver lipid profiles revealed that all biochemical parameters (TC, FC, TG, PL, and EC) were significantly reduced ($p < 0.01$) in the OeP & CsP-supplemented treated rats compared to the DC model rats (Figure 1b). Additionally, a significant increase in fecal TC levels was observed in the OeP & CsP-supplemented group when compared to the DC group (Figure 1c).



(a)



(b)



(c)

Figure 1 (a,b,c): Serum, liver and feces lipid profiles of control and experimental rats (M±SD).

NC: Normal Control ; DC: dyslipidemia control ; OeP and CsP sup ; *Oe*P : *Olea europaea* leaves powder ; *Cs*P : *Cynara scolymus* leaves powder supplement.*p<0.01.

Enzyme activity of LCAT, ApoA-I and ApoB-100

Chronic treatment with couscous enriched with leaves from OeP and CsP significantly increased levels of LCAT and ApoA-I in rats with dyslipidemia (p<0.01) compared to the DC group. In contrast, the rats treated with OeP and CsP supplements showed a significant reduction in ApoB-100 levels (p<0.01) compared to the other treatment groups, as indicated in Table 3.

Table 3: LCAT and Apo-lipoproteins levels of control and experimental rats (M±SD).

Parameters	NC (n=7)	DC (n=7)	OeP & CsP sup (n7)
LCAT (nmol/ml/h)	25.65±3,69	18.11±1.83	21.87±2.12*
ApoA-I (g/L)	1.53±0.06	0.30±0.03	1.67±0.04*
ApoB-100 (g/L)	0.47±0.01	1.77±0.01	0.35±0.01*

NC: Normal Control; DC: dyslipidemia control; OeP & CsP sup; *Oe*P : *Olea europaea* leaves powder ; *Cs*P : *Cynara scolymus* leaves powder supplement. *p<0.01.

Various biochemical parameters of different treated groups

Table 4 represents the fasting serum biochemical parameters. In rats treated with OeP & CsP sup, fasting blood glucose levels, creatinine, urea, AST, and ALT were significantly reduced (p<0.01) compared to the DC group. Additionally, uric acid levels in the OeP & CsP-sup group were decreased by 2%, though this reduction was not statistically significant. However, Albumin levels in the OeP & CsP-sup treated rats increased by 13%, also non-significantly.

Table 4: Various biochemical parameters among different treated groups of rats (n=7, M±SD).

Biochemical parameters	NC	DC	OeP & CsP sup
Blood glucose (mmol/L)	4.82±1.54	24.18±1.64	6.82±0.68*
Albumin (g/L)	33.18±4.39	31.74±6.32	35.93±4.98
Creatinine (µmol/L)	78.74±5.65	147.13±8.71	83.12±7.80*****
Urea (mmol/L)	4.19±1.70	9.49±3.74	6.74±1.55 *****
Uric acid (µmol/L)	145.30±3.00	150.60±2.87	147.87±2.77
AST (U/I)	29.11± 2.89	120.00±3.68	51.11±2.35*****
ALT (U/I)	31.01±1.79	89.75±2.05	36.31±3.33*****

NC: Normal Control; DC: dyslipidemia control; OeP & CsP sup ; OeP : Olea europaea leaves powder; CsP : Cynara scolymus leaves powder supplement. AST: Aspartate aminotransferase; ALT: alanine aminotransferase; *p<0.01.

DISCUSSION

Dyslipidemia, characterized by abnormal lipid levels in the bloodstream, is a significant risk factor for cardiovascular disease, and researchers predict that LCAT deficiency could be the possible cause of dyslipidemia and other conditions [23-24]. LCAT is a liver-secreted enzyme essential for the production of most plasma cholesteryl esters. It plays a pivotal role in reverse cholesterol transport (RCT), facilitating the formation and maturation of HDL. Deficiency in LCAT can hinder HDL maturation, resulting in free cholesterol accumulation in cell membranes and remnant lipoproteins in the plasma. Moreover, HDL is responsible for removing excess cholesterol from cells and delivering it to the liver for excretion. LCAT contributes to HDL remodeling and supports cholesterol homeostasis by esterifying FC on the surface of HDL, a process activated by apolipoprotein (apo) A-I, a key protein in HDL. Apo A-I is critical for maintaining HDL function, and its low levels are associated with reduced HDL and an increased risk of CVDs, atherosclerosis, CVD, dyslipidemia, and diabetes mellitus [25-27]. Consequently, LCAT activity is integral to cholesterol regulation and promoting cardiovascular health.

Various conventional medications are available for managing dyslipidemia and CVDs. However, many of these treatments can have adverse side effects. Consequently, researchers are exploring alternative remedies to address dyslipidemia and its related complications, such as CVDs. Plants and their derivatives have been used globally for centuries due to their rich sources of antioxidant as well as phytocompounds such as alkaloids, cardiac glycosides, flavones, flavonoids, steroids, tannins, terpenoids, and phenols [6-7, 14-15]. Two widely available plants, *O europaea* and *C scolymus*, are particularly noted for their effectiveness in treating various health conditions, including inflammation, oxidative stress, bile disorders, dyslipidemia, CVDs, hypertension, metabolic disorders, and cancer [9-11]. Therefore, this study was designed to investigate the effects of *O europaea* and *C scolymus* leaves powder supplements on a dyslipidemia model in rats fed a cholesterol and cholic acid diet.

The current study revealed that consecutive supplements of 1% *O europaea* and *C scolymus* leaves powder, showed a modest reduction (1.4%) of body weight, and food intake decreased by 3%. However, neither change was statistically significant compared to the DC group. However, hepatic total lipid levels were significantly reduced ($p < 0.01$) in comparison to the DC-treated rats (Table 2). Chiara Porro et al. (2024) stated that *Olea europaea* and *Cynara scolymus* leaves powder can

effectively reduce body weight and food intake in dyslipidemia rats because plants contain beneficial compounds that may help improve cholesterol levels as well as manage weight [28]. Various studies also suggested that *O europaea* & *C scolymus* leaves have strong hepatic lipid-lowering activity [29-30]. In the current study, lipid fractions were analyzed from serum, liver as well as fecal samples. After treatment with OeP & CsP-supplement serum TC, FC, TG, PL, and LDL-c were significantly ($p<0.01$) reduced and HDL-c was significantly ($p<0.01$) increased (Figure 1a).In addition, hepatic lipid profiles (TC, FC, TG, PL, and EC) were significantly ($p < 0.01$) decreased (Figure 1b) and fecal TC was significantly increased in the OeP & CsP-supplemented treated dyslipidemia rats (Figure 1c). The scientific community has discovered that *O europaea* and *C scolymus* leaves possess potent antioxidant properties, and antioxidants have lipid-lowering activities, which can mitigate dyslipidemia as well as cardiovascular disease [31-33].

Moreover, the study found that couscous enriched with leaves from *O europaea* & *C scolymus* were significantly ($p<0.01$) increased LCAT & ApoA-I levels (Table 3) and non-significantly increased (13%) serum albumin levels (Table 4). Previous studies supported that *C scolymus* and *O europaea* contain an enormous source of phytochemicals and antioxidants (total phenolics and oleuropein) that can significantly reduce TG and cholesterol levels while increasing HDL levels. This may increase LCAT levels positively and show various health benefits, including cardiovascular protection [34-36, 37].

Changes in liver biochemical markers may result from increased stress on the liver caused by the kidneys' inability to effectively eliminate toxic substances and poisons. Elevated liver enzymes like ALT and AST may be among these alterations. [38]. By contrast, OeP & CsP sup-treated rats showed a significant ($p<0.01$) reduction in ApoB-100 (Table 3), fasting blood glucose, creatinine, urea, AST, and ALT (Table 4) levels respectively. Cheurfa et al. (2019) demonstrated that alcoholic extracts of *O europaea* leaves have a hypocholesterolemic effect; they decreased TC, TG, LDL-c, and very low-density lipoprotein levels (VLDL), AST, and ALT indicating its hepatoprotective effects, likely due to its antioxidant properties, aligning with previous research [39], while increasing HDL [40]. Similarly, Ben Salem et al. (2022) showed that extract from *C scolymus* leaves exerted a cardioprotective effect in rats, leading to reductions in TC, TG, LDL-c, and atherogenic index, alongside an increase in HDL. Similarly, *C scolymus* leaves extract has demonstrated a cardioprotective effect in obese rats, with a reduction in total cholesterol, triglycerides, LDL-cholesterol, and atherogenic index, and an increase in HDL-cholesterol. Furthermore, *C scolymus* leaves extract has been reported to reduce plasma cholesterol in hypercholesterolemic adults [41].

CONCLUSION

The current investigation suggests that couscous made from Olea europaea and Cynara scolymus could serve as an effective substitute treatment for alleviating dyslipidemia and its associated complications. Both plants may help reduce significant levels of total cholesterol, free cholesterol, triglycerides, phospholipids, LDL cholesterol, ApoB-100, blood glucose, creatinine, urea, AST, and ALT, while also increasing levels of HDL cholesterol, LCAT, and ApoA-I. Further research is needed to clarify precisely these plants' exact mechanism of action.

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تأثير مضاد لاضطراب دهون الدم وتحسن نشاط إنزيم أسيليت ترانسفيراز الليسيثين–الكوليسترول (LCAT) بعد تناول مكمل غذائي يحتوي على مزيج من أوراق *Olea europaea* و *Cynara scolymus* في نموذج الفئران.

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ملخص

مقدمة: تنتشر نباتات *Olea europaea* (OeP) و *Cynara scolymus* (CsP) بشكل شائع في منطقة البحر الأبيض المتوسط، بما في ذلك الجزائر، وتستخدم تقليديًا لعلاج أمراض مختلفة، بما في ذلك اضطراب دهون الدم.

الهدف: استكشاف نشاط إنزيم الليسيثين–كوليسترول أسيليترانزفيراز (LCAT) في أوراق OeP و CsP باستخدام نموذج حيواني اضطراب دهون الدم ناتج عن نظام غذائي مسبب لفرط كوليسترول الدم في الفئران.

المواد والطرق: لتطوير نموذج حيواني لخلل دهون الدم، تم اختيار 21 جرذاً بالغاً من فصيلة Wistar وتغذيتها بنظام غذائي يسبب فرط كوليسترول الدم (2٪ كوليسترول و 1٪ حمض الكوليك) لمدة تصل إلى 15 يوماً. تم تأكيد اضطراب دهون الدم لدى الفئران من خلال الاختبارات الكيميائية الحيوية. بعد ذلك، تم إعطاء الفئران نظامًا غذائيًا غنيًا بمسحوق أوراق Oep و Csp (1٪) لمدة 15 يومًا من العلاج المتواصل. تحت تأثير تخدير البنتوباربيتال الصوديوم، تم جمع عينات الدم وتخزينها عند درجة حرارة −70 درجة مئوية لتحليلها كيميائيًا حيويًا.

النتائج: كشفت الدراسة أن أوراق Oep و Csp التي عولجت بها الفئران المصابة اضطراب دهون الدم خفضت بشكل ملحوظ FSG ($p<0.01$) و TC و FC و TG والفوسفوليبيدات و LDL-c و ApoB-100 والكرياتينين واليوريا و AST و ALT. على النقيض من ذلك، تحسنت المعلمات الكيميائية الحيوية الأخرى، بما في ذلك HDL-C و LCAT و ApoA-I، بشكل ملحوظ ($p<0.01$) مقارنة بالجرذان المصابة بخلل دهون الدم.

الاستنتاج: تخلص الدراسة الحالية إلى أن أوراق OeP و CsP لها تأثيرات خافضة للدهون ومضادة لخلل دهون الدم من خلال تعزيز نشاط LCAT في نموذج الجرذان المصابة بفرط كوليسترول الدم.

الكلمات الدالة: اضطراب دهون الدم؛ *Olea europaea*؛ *Cynara scolymus*؛ أسيليت ترانسفيراز الليسيثين–الكوليسترول؛ البروتين الدهني

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