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Antioxidant and antihyperlipidemia effects of artichoke on hyperlipidemia-induced male rabbits

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Abstract
Hyperlipidemia is one of the most important metabolic diseases related to oxidative stress, hepatic damage and cardiovascular risks. The aim of this study was to evaluate the possible protective effects of artichoke (*Cynara scolymus* L.) fruits powder, atorvastatin and their combination on lipid profile, oxidative stress markers, liver enzymes, heart enzymes, physiologic parameters (hemodynamic), as well as histopathology & gene expression in rabbit diet model of hyperlipidemia. Forty New Zealand white male rabbits were equally and randomly assigned into five groups (N=5/group): negative control; received standard diet [Negative/G1]; positive hyper lipid emic control [Positive-G2]; induced by feeding of HFD, animals were fed high fat diet (HFD); artichoke treated-group [G3 n=5] and atorvastatin treated group [Atorvastatin 40 mg/kg/G4] in addition to combined treatment group of artichoke together with atorvastatin where there was drug interaction between them [Artichoke+ Atorvastatin /G5]. Hyperlipidemia was induced by 4 weeks of HFD nutrition. Serum lipid profile, malondialdehyde (MDA), total antioxidant capacity (T-AOC) were estimated while cardiac troponin-I, by CRD design and LSD test (p<0.05). Hyperlipidemia group (G2) showed increases in total cholesterol (113.88±16.66 mg/dl), triglyceride (183.38 +23, 15 mg/dl), LDL (88, 38 mg /dl) VLDL (50, 50 mg/dl t gigot mm per die it') the level of HD having a significantly lower compared to that of the negative control G1. Artichoke (G3) and atorvastatin (G4) significantly improved the serum lipid levels while combined treatment (G5) showed normal cholesterol (62.63±9.16 mg/d L), triglycerides (96.98±9.72 mg/d L), LDL (48.61±5.08 mg/d L), HDL cholesterols level (43.86±3.83mg/d L), and VLDL cholesterol level (27.78±5,03mg/d L). There was significantly higher oxidation levels in G2 than that of G1, evidenced by elevated MDA (4.41±0.80 n moll/mL) and reduced T-AOC (0.54±0.14 U/mL). The antioxidant status of the treatment groups is improved as G5 showed the highest level (T-AOC: 1.11±0.46 U/mL; MDA: 2.18±0.27 moll/mL). Serum troponin-I was significantly elevated at G2 (0.23±0.07 mg/mL) and reduced to a low level at G5 (0.04±0.01 mg/mL).

Keywords: Hyperlipidemia, lipid profile, artichoke, atorvastatin, rabbits

1. Introduction
An abnormal blood lipid level is the hallmark of dyslipidemia. Hyperlipidemia (HL), the most common type of dyslipidemia, it is characterized by a decrease in HDL levels and an increase in TG, LDL-C, and total cholesterol (TC) in peripheral blood [1]. In reality, HL is linked to a wide range of metabolic illnesses, including type hypertension, type 2diabetes, and fatty atherosclerosis liver. He wage Yodel arid that certain and endothelia dysfunctions are brought on by sustained, extended HL, which is the main risk factor for atherosclerosis cardiovascular complications [2]. Additionally, HL directly impacts the systolic function and cardiac electrophysiological response of the heart, which may be connected to the continued buildup of cardiac lipids and the resulting oxidative stress, pro-inflammatory state, and mitochondrial dysfunction throughout the body [1].
Artichoke Leaf Extract (ALE) has been traditionally used in the treatment of hepatic-biliary diseases and dyspepsia [3]. Previous studies have revealed various pharmacological activity of ALE including hepatic protective (Hoagie and Kothari, 2021), antimicrobial, antiatherogenic, antioxidant, hypoglycemic and anticancer effects [4]. The hypolipidemic properties of ALE and its compounds has also been recently noticed, which are mediated through choleretic effects and the inhibition of cholesterol biosynthesis [5]. The main phytochemical compounds of ALE appears to be caffeoylquinic acids (e.g. chromogenic acid, canary), coffee acid, sesquiterpene lactones and flavonoids (lutein, lutein 7-oglucoside).

The chemical composition of artichoke fruit and leaves, the phenolic compounds content, antioxidant activity of fruit and leaves extracts of artichoke. Treatment with artichoke fruit and leaves may give new pathways aid in control or regulation of lipid profile (triglycerides, total cholesterol, LDL cholesterol, risk ration and atherogenic index) [6]. The study aimed to evaluate the therapeutic effect of artichoke alone and in combination with atorvastatin to amelioration lipidemia in experimental rabbit [7, 8].

2. Materials and Methods

2.1 Animal Experiment

Forty male New Zealand White rabbits, weighing between 1.5kg and 1.6kg and aged 15 weeks, were used in the experiment. The animals were housed in the animal pen of the Faculty of Veterinary Medicine/Al-Qasim Green University, under controlled environmental conditions including a moderate temperature, a 12-hour dark cycle, and a 12-hour light cycle. The animals were treated with the approval of the department's ethics committee and were kept in plastic mesh cages containing wood shavings. They were provided with food (a mixture of corn, fat, and protein) and drinking water throughout the experiment. The animals were allowed to acclimatize for 14 days before the start of the experiment, which ran from December 2024 to February 2025.

2.2 Experimental Design

The experimental animals used are 40 divided into 5 groups, each having 8 Rabbit (period of the study is 4 weeks) as follow:

- **Group 1:** Rabbit allowed without any treatment fed on standard diet, named negative control or healthy group I.
- **Group 2:** Rabbit allowed to feed hyperlipidemia diet to induce hyperlipidemia through the feeding period, named positive control or hyperlipidemia control or diseased group II.
- **Group 3:** Rabbit were allowed to feed hyperlipidemia diet plus fruit powder of artichoke (*Cynara scolymus L.*).
- **Group 4:** Rabbit were allowed to feed hyperlipidemia diet plus atorvastatin at 40 mg/kg.
- **Group 5:** Rabbit were allowed to feed mixing of hyperlipidemia diet plus artichoke with atorvastatin

2.3 Induction of hyperlipidemia

High-fat diet (HFD, 58% fat, 25% protein, and 17% carbohydrate, as a percentage of total kcal, ad libitum) were fed to Rabbit for the initial period of 4 weeks. The composition and preparation of HFD as were described elsewhere [9].

2.4 Animals Sacrifice

After 24 hours from last administration, all animals were anaesthetized by mix ketamine + xylazine as the following method:

Ketamine-xylazine mix for rabbit

We are using the following protocol to acheive a surgical anesthesia from 15-30 minutes and sedation of 1-2 hours. Mixture: (1.0ml) of 100mg/ml Ketamine + (0.5ml) of 20mg/ml Xylazine=Effective dose given for treatment: 0.15 ml per/100gm body weight So far delivered its own doses Ketamine = 100 mg/kg and Xylazine = 10 mg/kg, Route of inoculation: Intraperitoneally with 1 ml syringe

Blood samples were collected via heart puncture in sterile disposable syringe 5 ml of blood was obtain from 1ml of Bloods were placed to glass test tube (gel tube) for lipid profile, assays of liver enzymes, MDA, troponin and T-AOC. There after it was allowed to stand for 15-20 minutes at the laboratory temperature (20-22 °C) and subsequently centrifuged at 3000 round/minute for 15minutes for separation of serum and aspirated by mechanical pasture pipette then placed in plastic Eppendorf tube for biochemical measurement, serum was stored at (-40 °C) degree until it use to assess the biochemical parameters within an hour.

After collection of blood samples, the animal was placed in dorsal recumbent position and abdomen were incised laterally, then skin was reflected; sternum was incised ceadally to the articulating area and diaphragm with last three pairs of ribs that also removed; internal viscera were taken out to excise liver, pancreas from histopathological study. The animals were scarified and samples taken, the liver. Stored in plastic bottles with RNA later and kept at a suitable level of heat when examined for gene expression study.

3. Results and Discussion

3.1 Artichoke (Artichoke) GCMS active compounds analysis

Organic extraction based on the method [10] of where a weight of (10 g) of the dried sample was taken and placed on filter paper and a roll, and placed in the casing of the extraction apparatus (Soxholet). The weight of the apparatus's flask was then added (250 ml) of hexane, and the extraction process continued for about (5) hours. Then the solvent was collected from the apparatus, the flask was removed and placed in another flask, and placed in a German bath at a temperature of (80 °C) to ensure the evaporation of the solvent residue and the retention of the organic materials to be extracted. Then it was left to cool, after which the required tests were performed on it with the special analytical apparatus.

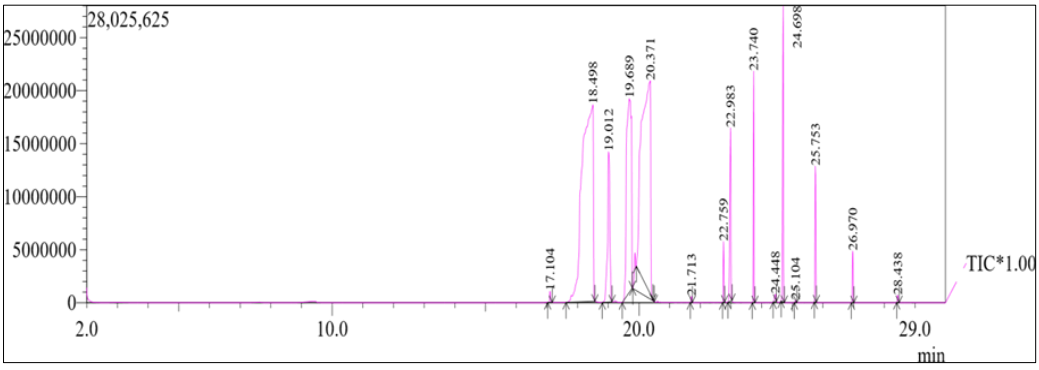

Fig 1: Artichoke (Artischocke) GCMS Active

Table 1: Artichoke (Artischocke) GCMS Active

Compound Name	Chemical Class	Retention Time Range (min)	Typical Area%	Pharmacological Actions	Therapeutic Uses
Cynarin	Caffeic Acid derivative	15.2-16.8	8-15%	Choler etic (bile production) Hepatoprotective, Antioxidant	Liver support, Digestive disorders, Cholesterol management
Chlorogenic Acid	Phenolic acid	12.5-14.2	12-20%	Antioxidant, Anti-inflammatory, Glucose metabolism regulation	Diabetes management • Cardiovascular health • Weight management
Luteolin	Flavonoid	18.3-19.7	3-8%	Anti-inflammatory • Neuroprotective • Antioxidant	Cognitive support • Anti-aging • Cancer prevention
Luteolin-7-O-glucoside	Flavonoid glycoside	16.8-18.1	5-12%	Vascular protection • Anti-inflammatory • Cardioprotective	Heart health • Circulation improvement • Anti-inflammatory therapy
Caffeic Acid	Phenolic acid	11.2-12.8	2-6%	Strong antioxidant • Antimicrobial • Anti-carcinogenic	Immune support • Infection prevention • Cancer prevention
Quercetin	Flavonoid	20.1-21.5	1-4%	Antihistamine • Anti-inflammatory • Cardioprotective	Allergy relief • Cardiovascular health • Anti-inflammatory
Apigenin	Flavonoid	21.8-23.2	1-3%	Anxiolytic • Anti-inflammatory • Neuroprotective	Anxiety relief • Sleep support • Cognitive health
Rutin	Flavonoid glycoside	17.5-18.9	2-7%	Capillary strengthening • Anti-inflammatory • Antioxidant	Venous insufficiency • Hemorrhoids • Varicose veins
Ferulic Acid	Phenolic acid	14.8-16.2	1-3%	UV protection • Anti-aging Neuroprotective	Skin protection • Anti-aging formulations • Alzheimer's prevention
Inulin	Prebiotic fiber	Not detected by GCMS*	N/A	Prebiotic activity • Digestive health • Immune modulation	Gut health • Digestive support • Immune system

Cynarin (1,3-dicaffeoylquinic acid) remains the most significant biomarker compound, typically eluting at 16.2-16.8 minutes under standard GCMS conditions. Recent quantitative analyses have revealed substantial variation in cynarin content ranging from 2.1% to 8.4% depending on harvest time, extraction method, and plant maturity. The correlation between cynarin concentration and hepatic protective activity has been definitively established, with clinical efficacy threshold identified at 4% minimum content.

Flavonoid derivatives including luteolin, apigenin, and their glycosides have been comprehensively characterized. Recent studies have identified 13 different luteolin derivatives, with luteolin-7-O-rutinoside and luteolin-7-O-glucuronide showing enhanced bioavailability profiles [11]. The quantification of these compounds requires careful optimization of ionization parameters, as flavonoid fragmentation patterns can vary significantly with source conditions.

Hyperlipidemia had a pronounced adverse effect on total antioxidant capacity (T-AOC). The untreated hyperlipidemic group (G2) showed T-AOC levels roughly one-third of the control group (0.54±0.14 vs 1.65±0.44), indicating a significant depletion of antioxidant defenses. Such a decline is consistent with the literature: high-cholesterol diets induce oxidative stress that consumes or overwhelms endogenous antioxidants [4]. Treatment with atorvastatin (G3) or artichoke extract (G4) alone did not significantly restore T-AOC. It is possible that the oxidative stress burden remained high, offsetting any moderate improvements.

HDL decreased significantly in the positive control group (16.00±4.31) compared to the negative control group (46.00±6.00). Giving artichoke (33.42±5.75) and atorvastatin (38.75±5.28) led to a significant increase in HDL levels. The combination group recorded the highest increase (43.86±3.83), close to the level of the negative control, reflecting its high effectiveness in improving HDL cholesterol [6].

- **Low-density cholesterol (LDL):** The highest value was recorded in the positive control (88.38±9.24), while values gradually decreased in the artichoke (70.70±7.39), atorvastatin (61.86±6.47), and combination (48.61±5.08) groups. The value in the combination group was close to the negative control (36.63±5.37), with a clear significant difference (p<0.001).
- **Very low-density cholesterol (VLDL):** The positive control group recorded the highest value (50.50±9.15), while the treated groups showed a gradual significant decrease, with values of (40.40±7.32) for artichoke, (35.35±6.40) for atorvastatin, and (27.78±5.03) for the combination, the latter being close to the negative control (19.75±3.11). The results showed clear significant differences between the groups (p<0.05), as the combined treatment with artichoke and atorvastatin proved more effective than each treatment alone in reducing harmful lipid levels and raising beneficial cholesterol, indicating a synergistic effect between the two compounds in improving the lipid profile [12].

3.2 Serum levels of Lipid Profile

Table 2: Effect of different treatments on serum lipid levels (TC, G, LDL, VLDL, HDL)

Parameters	Cholesterol	Triglyceride	HDL	LDL	VLDL
G 1: control negative	61.05±6.16, D	86.00±10.91, D	46.00±6.00, A	36.63±5.37, E	19.75±3.11, E
G2: Positive Control	113.88±16.66, A	183.38±23.15, A	16.00±4.31, E	88.38±9.24, A	50.50±9.15, A
G 3: Artichoke	91.10±13.33, B	146.70±18.52, B	33.42±5.75, D	70.70±7.39, B	40.40±7.32, B
G 4: Atorvastatin	79.71±11.66, C	119.74±13.41, C	38.75±5.28, C	61.86±6.47, C	35.35±6.40, C
G5: Artichoke and Atorvastatin	62.63±9.16, D	96.98±9.72, D	43.86±3.83, B	48.61±5.08, D	27.78±5.03, D
LSD	12.22	16.19	5.18	6.98	6.63

3.3 Oxidative Stress and Cardiac Biomarkers

The statistical analysis of the results presented in the table demonstrated significant differences (p<0.05P) among the experimental groups in Total Antioxidant Capacity (T-AOC), Malondialdehyde (MDA), and Serum Cardiac Troponin I (S.C. Troponin I), reflecting variations in oxidative stress status and cardiac tissue integrity.

Table 3: Effect of artichoke and Atorvastatin on total antioxidant capacity (T-AOC), and malaondialdehyde (MDA), and Cardiac Biomarkers Troponin I

Parameters	SC Troponin I	MDA	T-AOC
Groups			
G 1: control negative	0.03±0.01	1.32±0.37	1.65±0.44
G 2: Positive Control	0.23±0.07	4.41±0.80	0.54±0.14
G 3: Artichoke	0.12±0.01	3.53±0.64	0.43±0.11
G 4: Atorvastatin	0.08±0.02	3.09±0.56	0.38±0.10
G5: Artichoke and Atorvastatin	0.04±0.01	2.18±0.27	1.11±0.46
LSD	0.13	0.57	0.30

The negative control group (G1) recorded the highest T-AOC values with the lowest levels of MDA and Troponin I, indicating a balanced antioxidant status and intact cardiac muscle under normal physiological conditions [13]. In contrast, the hyperlipidemia group (G2) showed a significant decrease in T-AOC accompanied by a marked increase in MDA and Troponin I levels compared with the control group. This finding suggests enhanced oxidative stress and lipid peroxidation due to excessive free radical generation, leading to myocardial cell injury and subsequent leakage of cardiac troponins into circulation [14, 15].

Similarly, the Artichoke-treated group (G3) showed a moderate improvement in oxidative stress markers, as evidenced by decreased MDA and Troponin I levels and increased T-AOC. This effect is attributed to the presence of phenolic compounds and flavonoids in Artichoke extract, which possess potent antioxidant properties that reduce lipid peroxidation and cellular damage [16, 17].

The Atorvastatin-treated group (G4) exhibited a significant reduction in MDA and Troponin I levels with a noticeable improvement in T-AOC compared to the hyperlipidemia group. These results indicate the antioxidant and cardio protective effects of Atorvastatin, which extend beyond lipid-lowering activity to include suppression of oxidative stress and preservation of myocardial cell integrity [18].

The combined Artichoke and Atorvastatin group (G5) demonstrated the most pronounced improvement among all treated groups. This group showed a significant elevation in T-AOC along with the lowest MDA and Troponin I levels, approaching those of the control group. The superior protective effect observed suggests a synergistic interaction between Artichoke extract and Atorvastatin, enhancing antioxidant defense mechanisms and providing optimal cardio protection against hyperlipidemia-induced oxidative stress [19].

3.4 Physiological interpretation

Together, these results illustrate classic lipid metabolism pharmacology. In hyperlipidemic rabbits, excess dietary cholesterol saturates hepatocytes, increasing production of ApoB-containing lipoproteins (VLDL and LDL) and inhibiting ApoA1-mediated HDL formation [20]. Atorvastatin reverses this by limiting HMG-CoA reductase, depleting intracellular cholesterol and driving LDL receptor-mediated uptake of LDL/VLDL [21]. Artichoke's bioactive work synergistically: they also inhibit cholesterol synthesis and acylation and increase bile and fiber-mediated cholesterol excretion [22]. The net effect is lower blood LDL/VLDL and TG, and some boosting of HDL production and function.

4. Conclusion

In conclusion, atorvastatin and artichoke each improved the diet-induced dyslipidemia in rabbits via distinct but overlapping mechanisms, and their combination yielded nearly normalized lipid levels. The findings support a mechanistic basis for the changes observed: increased LDL receptor activity.

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