The protective effect Cicer arietinum ethanolic extract in comparison to rosuvastatin on the hyperlipimic female rats

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Abstract
The current study aimed to detect of the protective effect of the Cicer arietinum seed extract to reduce the levels of inducted hypercholosteremia in adults' female rats that induced by triton X-100 in comparsion to rosuvastatin. Thirty female rats were equally separated into five groups and treated for (28 days). The first group termed G1 treated with distilled water which was negative control group, the second one G2 treated with triton X-100 at dose (100 mg/kg) I.P positive control group, the third group G3 treated with Cicer arietinum crude extract at dose 349.015 /kg B.W after induction with triton X-100, the fourth group G4 treated with rosuvastatin after induction with triton X-100. And the last group treated with combination of Cicer arietinum extract with rosuvastatin after induction with triton X-100. The result of lipid profile (total cholesterol, triglyceride, very low-density lipoprotein, low density lipoprotein and high-density lipoprotein) for G2 showed significant elevation when matched with negative control group except the HDL which showed significant inhibition in level. While the G 3 revealed significant decrease in lipid profile with significant rise of HDL levels as compared with G 4 and G2. Furthermore, the G4 group showed significantly decrease in lipid profile results when matched to G2. The result of G5 showed significant decrease in lipid profile with rising of HDL when compared with all other groups. Whereas the Gamma glutamate transferase (GGT) levels of G3 showed significant decrease comparing to G2 that revealed significant increase in. While the G4 showed no significant decrease comparison to G2. Furthermore the histopathological section of G2 after intraperitoneal administration of triton X- 100 the liver cross section revealed presence of fatty change inside liver cells with blood vessels congestion, presence of bi nucleated hepatocytes, inflammatory cells infiltration and conclusion body, with presence of vacuolar degeneration and hepatocytes cells necrosis but G3 histopathological changes tend to return to the normal state with presence of bi nucleated hepatocytes cells and mild mononuclear cells infiltration in addition to kupffers cells proliferation G4showed portal artery congestion and inflammatory cuffing and multiple aggregation mononuclear cells around blood vessels. While G5 revealed mild mononuclear cells infiltration in addition to kupffers cells proliferation and mild congested blood sinuses as displayed, congested central vein, conclusion: Cicer arietinum have great capacity to correct the dyslipidmic state with protection of hepatic cells and decrease the liver elevated enzymes
Keywords: triton X100, Cicer Arietinum, rosuvastatin, hyperlipidemia and rat.

1. Introduction

Hyperlipidemia is one of terms that covered many abnormal elevated lipid state like presenting of high fats, or increasing cholesterol and triglycerides inside the living bodies (1). This disorder can associate to induce many other diseases like atherosclerosis stroke and diabetes mellitus (2). Many different classifications of drugs can be used in order to control fats levels inside the body. The most usable class called statin group including rosuvastatin. Many different classification of drugs can be used in order to control fats levels inside the body. The most usable class called statin group including rosuvastatin
Which is strong competitor of the "3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase" the key rate-limiting enzyme for pathway of cholesterol biosynthesis. Result in the suppress of intracellular cholesterol formation (3). Even with great therapeutic effect of rosuvastatin as lipid lowering drug approved by FDA but still has many dangerous side effects can cause severe problems, rosuvastatin can cause muscular pain that ranged from myalgia without an increase in muscle enzymes to significant myopathy with muscular pain and weakness as well as an increase in muscle enzymes (myositis), and finally the most severe form of rhabdomyolysis,it also had been found that rosuvastatin can decrease renal function (4). It found also linked to a higher risk of diabetes than moderate-intensity statins. (5). In addition to that liver dysfunction may be caused as a result of using statin drugs (6). For all these side effect recently all research try to found another natural source to replace with .Cicer arietinum one of the legumes that showed at phytochemical analysis for presence of Carbohydrates, proteins, amino acids, fixed oils, phytosterols, alkaloids, Polyphenolic compounds and tannins, glycosides, saponins, amino acids, iron, phosphate, sulfate, and sodium were found in Cicer

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arietinum seeds and there is also biochanin and legumin can be extracted from seeds of Cicer arietinum (7). For that Cicer arietrinum had aphrodisiac, antioxidant, anti-inflammatory, Anticancer, hepatoprotective, anti-hyperlipidemia activity and a variety of other pharmacological actions (8).

2. Materials and Methods

Animals: This study was carried out at the College of Veterinary Medicine/University of Baghdad Department of Physiology, Biochemistry and Pharmacology. Thirty mature female rats, 3 months old and weighing 197-210g, were housed in an appropriate habitat with a temperature range of (22-25 °C). For acclimatization, the rats were kept in plastic cages measuring 45x20 x15 cm in an animal house around 3 weeks before the experiment started. They were fed with normal pellets with tap water

Ethanolic extraction: One kilogram of Cicer arietinum, carefully rinsed with tap water to eliminate any foreign bodies might be suspended in the Cicer arietinum and then soaked in two liters of distilled water to ensure that no foreign bodies are present, then allowed to dry for three days at room temperature (9). Cicer arietinum seed crushed into a fine powder. The extraction of Cicer arietinum seeds performed by the Soxhlet apparatus using 70 percent ethanol and 50 centigrade temp. Cicer arietinum seeds, dried powder, placed in a thimble portion in weight (70 gm) and placed in the extraction unit of the apparatus, in a round bottom flask, 500 mL of 70 percent ethanol was added, and extraction began at 50 c temperature. The extraction process ended until clear and colorless solvent appeared in the extraction unit. The extract was then filtered and evaporated to dryness for 3 hours in a rotary evaporator at 40 degrees Celsius and 200 spins per minute. The extract was then placed in an incubator at 40 degrees Celsius for 12 hours until the alcohol evaporated, and the extract became a thick semi-solid mass with a dark yellow color, after which it was stored in a glass container with a plug-in refrigeration. (10).

Experimental design: thirty adult female rats were separated into five groups equally and medicated orally by stomach tube for a period twenty-eight days as following:

First group (G1): six female rats were treated with distilled water only, (negative control group).

Second group (G2): six female rats were medicated with triton X-100 (100mg/kg/B.W.) (Positive control group).

Third group (G3): six adult female rats were medicated with triton X-100 followed by Cicer arietinum extract at dose (349.015mg/kg).

Fourth group (G4 six adult female rats were medicated with triton X-100 followed by Rosuvastatin at dose (1.77mg/kg).

Fifth group (G5) six adult female rats were medicated with triton X-100 followed by Cicer arietinum extract at dose (349.015mg/kg) and Rosuvastatin at dose (1.77mg/kg) combination.

Preparation of Stock Solutions, Concentrations, and Doses: Stock solutions of Cicer arietinum seeds crude extract at doses (100, 200, 300, 400 and 500) mg/ kg, the concentrations of solutions were (50, 100, 150,200 and 250) mg/ml respectively and the dose then adjusted according to body weight of female rats for that each 0.2 ml of extract stock solution given to each 100 gm of rat body weight by stomach tube.

Rosuvastatin: The recommended human dose of rosuvastatin 20 mg/day. daily dose for treating hyperlidimic disorder according to (11). The rosuvastatin was given orally at dose 1.77mg/kg to the rats after converted human dose 0.28 mg/kg to animal dose by multiplying the human dose by rat factor 6.2 (12), the concentration of solution was 0.885mg/ml, furthermore, 0.2ml of stock solution of rosuvastatin was given orally to each 100gm of rat body weight by stomach tube.

Determination lipid profile (total cholesterol, triglycerides, low density lipoprotein, very low-density lipoprotein and high-density lipoprotein: From each animal in every group, blood was taken. Typically, from the heart of the animal are used to draw blood. The quantitative analysis method of Giesses diagnostic kit was used for measuring the lipid profile concentrations in each control and treatment groups. According to (13)

Determination Gamma glutamate transferase (GGT): The Szasz process had been modified by the GGT procedure. Gamma-glutamyl-3-carboxy-4-nitroanilide is the substrate, and GGT catalyzes the transfer of the gamma-glutamyl group to glycylglycine to produce 5-amino-2-nitrobenzoate. The synthesis of 5-amino-2-nitrobenzoate was caused the shift in absorbance at 410/480 nm, and it was directly correlated with the sample's GGT activity. The tests were carried out by using of Giesse according to (14).

Histopathological study Liver samples were taken out of the body and cleared off from the implicated connective tissue and fat, then stored in 10% formalin for fixation, and processed on a regular basis. histokinette, microtome cut off at 5m-6m density, stained with Haematoxylin and eosin, and the samples were then examined under a light microscope (15).

3. Statistical Analysis

Data were statistically analyzed using one way analysis of variance (ANOVA) with a significant threshold of (p0.05). Least Significant Differences were used to determine differences between a certain group (LSD)

4. Results and Discussion

The results in a table (1) revealed that the concentrations of total cholesterol (TC), triglycerides

(TG), very low density lipoprotein (VLDL), and low density lipoprotein (LDL) of the G2 clarified a significant increase (P≤0.05) in mean values (168.40±1.12, 105.40±1.03, 21.08±0.20, 106.84±1.55and 40.48±0.75) respectively in comparison G1with mean value (146.00±3.30, 83.60±0.92, 16.72±0.18, 65.42±2.69)and all other treated groups .While the HDL concentration was considerably lower significantly (P≤0.05) in G2 with mean value (40.48±0.75) when compared to all treated groups and control negative group. While the results of total cholesterol, TG, VLDL, and LDL lipoproteins of the animals treated with the G3 seeds crude extract group showed a significantly reduction in (P≤0.05) with mean values (151.20±1.28, 89.40±1.43, 17.88±0.28 and 77.98±1.32) respectively as compared with G4 treated group and G2 group. While the HDL levels of G3 showed a significantly increase (P≤0.05) with mean value (53.34±0.58) during comparing with G4 and G1. In another hand the TG, VLDL, and LDL lipoproteins of G4 group showed significantly decrease (P≤0.05) in mean value (153.80±1.85, 93.40±0.92, 18.68±0.18 and 81.78±2.36) when compared with G2 with no significant difference with G3 of female rats. The result of the total cholesterol, TG, VLDL, and LDL lipoproteins G5showed significant decrease (P≤0.05) when compared with all other groups in mean values (148.40±1.43, 83.00±1.22, 16.60±0.24, 73.60±1.21,). while HDL (58.20±0.70 As showed in a table (1)

Table (1) Effect of Cicer arietinum extract, rosuvastatin drug and Cicer arietinum with rosuvastatin combination on lipid profile (mg/dl) levels of female rat for 28 days of treatment.

Groups	Cholesterol (mg/dl)	TG (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
G1	146.00±3.30c	83.60±0.92d	16.72±0.18d	65.42±2.69d	63.86±0.81a
G2	168.40±1.12a	105.40±1.03a	21.08±0.20a	106.84±1.55a	40.48±0.75d
G3	151.20±1.28bc	89.40±1.43c	17.88±0.28c	77.98±1.32bc	53.34±0.58c
G4	153.80±1.85b	93.40±0.92b	18.68±0.18b	81.78±2.36b	55.34±0.97c
G5	148.40±1.43bc	83.00±1.22d	16.60±0.24d	73.60±1.21c	58.20±0.70b
LSD	5.79	3.32	0.66	5.66	2.34

Means with a different small letter in the same column are significantly different (P<0.05), *G: control negative group, G: control positive triton x-100 group, G: *Cicer arietinum* extract treated group, G: rosuvastatin treated group, G: *Cicer arietinum* and rosuvastatin treated group. *n=

Gamma glutamate transferase (GGT): The results in a table (2) revealed that the concentrations obtained for gamma glutamate transferase (GGT) for G2 showed a significant increase (P< 0.05) and the mean value was (4.40±0.40) during the comparative G1 and all other treated groups. While G3 treated female rats showed a significant decrease (P< 0.05) respectively in mean value (3.50±0.24) when compared to G2 and G4 treated groups with mean values (4.40±0.40 and 4.10±0.58) respectively. Furthermore, the G4 animals showed no significant differences when matched with G2 and other treated groups. While the G5 of Cicer arietinum with rosuvastatin showed significant decrease (P<0.05) in comparison to G2 and G4 treated groups.

Table (2) Effect of Cicer arietinum extract, rosuvastatin drug and Cicer arietinum with rosuvastatin combination on gamma glutamate levels (U/l) of female rat for 28 days

Group	GGT (u/l)
G1	2.60±0.50c
G2	4.40±0.40a
G3	3.50±0.24ab
G4	4.20±0.58ab
G5	3.70±0.58c
LSD	1.42

Means with a different small letter in the same column are significantly different (P<0.05), *G: control negative group, G: control positive group, G: *Cicer arietinum* extract treated group, G: rosuvastatin treated group, G: *Cicer arietinum* and rosuvastatin treated group. *n=6

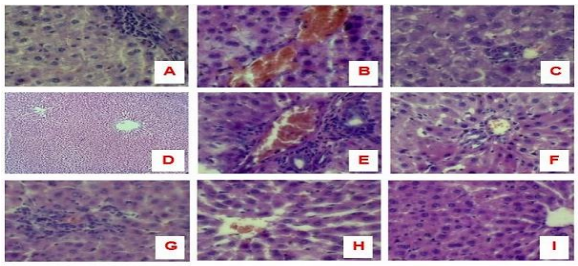

Fig (1) shows cross section of liver histopathology for

Histopathological study: The histopathological section of G2 after intraperitoneal administration of triton X- 100 the liver cross section revealed presence of fatty change inside liver cells with blood vessels congestion, presence of bi nucleated, hepatocytes inflammatory cells infiltration and conclusion body, with presence of vacuolar degeneration and hepatocytic cells necrosis as shown in figures (3.A and 3B). While the liver section of G3 treated animals showed again tend to be normal cross section with normal hepatocytes cells addition to presence of bi nucleated hepatocytes cells and mild mononuclear cells infiltration in addition to kupffers cells proliferation as shown in figure (3.C and 3D) in the liver cross section of G4, the result of histopathological cross section of the liver have been showed portal artery congestion and inflammatory cuffing and multiple aggregation mononuclear cells around blood vessels as shown in figures (3.E and 3 F). The last treated group G5 revealed mild mononuclear cells infiltration in addition to kupffers cells proliferation and mild congested blood sinuses as displayed, congested central vein as in figures (3. G and 3.H). The histopathological results in the liver sections of the negative control group revealed normal histological structure, normal hepatocytes cells as shown in (3.I).

5. Discussion

The increase in levels of lipid profile while the high-density lipoprotein falling down may be resulted by triton X-100 which increasing of cholesterol synthesis inside the liver cells, it also has the ability to promote absorption of lipids from gastrointestinal tract by emulsification of lipids making there absorption too much easier (16). The animal treated with *Cicer arietinum* showed noticeable improvement in levels of lipid profile with it's highly content of dietary fiber and very low lipids concentrations it also enhanced HepG2 cells' for absorption of extracellular cholesterol which called Free cholesterol resulted in improve of lipid profile (17) it also contain phenols which decrease lipid absorption(29) .there is evidence revealed peptide (VFVRN) had been discovered in the *Cicer arietinum* VFVRN had capacity to decrease cholesterol by reducing the expression and activity of HMG-CoA, a crucial enzyme in cholesterol production (18).while rosuvastatin which is chemical fully synthetic drug competed with HMG co A reductase stopping cholesterol synthesis (19). And enhancing of liver cells to increase LDL receptor to increase lipids break down (20). the combination can make a synergistic effect with minimization of possible side effect. Rise of GGT to G2 may be resulted from consequence of Triton-induced hyperlipidemia, which damaged hepatocytes by causing fat to penetrate them (21). Furthermore, the fats can accumulate in hepatocytes led to liver dysfunction by direct cellular cytotoxicity, lipid peroxidation, mitochondrial dysfunction, oxidative stress leading to raise in GGT levels, (22). While *Cicer arietinum* seeds plant extract the GGT levels inhibited and this may be attributed to antioxidant properties of *Cicer arietinum*, as well as the *Cicer arietinum* had the ability in an enhancement of catalase activity, resulting in a considerable drop in oxidative stress indices (23). In the rosuvastatin treated group showed no improvment in GGT levels and this may be associated with liver injury that caused by creation of a harmful, unimportant drug metabolism intermediate formed during the metabolism with CYP 2C9 system (24). Furthermore, rosuvastatin liver injury by autoimmune mechanism activation (25). In addition to that rosuvastatin can be caused aminotransferase leakage by disruption to mitochondrial membranes (26). The combination of the *Cicer arietinum* with rosuvastatin drug revealed an improvement of the gamma glutamate enzymes and this result may be regarded to the role of *Cicer arietinum* in decreasing of the side effects of rosuvastatin. In histopathological study of G2 the necrosis caused by oxidative stress (30). while *Cicer areitinum* showed improvement may be resulted from capability of seeds of *Cicer arietinum* extract to inhibit the oxidative stress action on liver cells, and ability to raise the capacity of the catalase activity with lowering of liver enzyme activity (23). As well as the ability of the *cicer* arietinum to improve the lipid profile and regulating of blood triglycerides may be helped in improving the liver cells (27). rosuvastatin can be harmful to liver due to its mostly processed by the liver and raise aminotransferases levels, with chance of hepatic potential toxicity that resulted from change of the hepatocyte cellular membrane or by direct liver damage (28). Furthermore, rosuvastatin could be interacted with the proteins and enzymes of the hepatic interstitial tissue by interfering with the antioxidant defense mechanism and causing the production of reactive oxygen species (ROS), which in turn could also be mimic an inflammatory response , this result agreed with (29), The dilation of the central vein may be a sign that rosuvastatin is had an impact on the permeability of the hepatocyte and endothelial cells membranes in the blood vessels and hepatocytes enlarge.

6. Conclusion

triton X-100 induce hyperlipidemia by increase lipid absorption from G.I.T, with prevention of liver from utilizing lipids. *Cicer arietinum* had the ability to correct lipid profile and protect hepatic cells against oxidative stress induced by triton and normalize the hepatic histology with inhibition of gamma glutamate levels.

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