Biochemical effects, hypolipidemic and anti-inflammatory activities of Artemisia vulgaris extract in hypercholesterolemic rats

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The purpose of the present study was to investigate hypolipidemic and anti-inflammatory effects of Artemisia vulgaris extract in hypercholesterolemic rats. Hypercholesterolemia was induced by feeding of rats with high fat diet containing 3% cholesterol in olein oil, for 8 weeks. Feeding of rats with high fat diet for 8 weeks, leading to a significant increase in serum triglycerides, total cholesterol, low density lipoprotein cholesterol, malondialdehyde and nitric oxide, tumor necrosis factor-α levels and a significant decrease in serum high density lipoprotein cholesterol level, liver hydroxymethylglutaryl-CoA reductase activity and paraoxonase-1 activities as compared to the normal control group. Treatment of high fat diet rats with Artemisia vulgaris extract for 4 weeks at a dose of 100 mg/kg per day, resulted in normalized serum lipid profile, a significant increase in paraoxonase-1 activity and decrease in serum malondialdehyde, nitric oxide and tumor necrosis factor-α level as compared to high fat diet-treated animals. Also the extract caused a significant decrease in hydroxymethylglutaryl-CoA reductase activity and paraoxonase-1 activities as compared with both high fat diet-treated animals and control ones. In conclusion, Artemisia vulgaris extract has hypolipidemic, anti-inflammatory, antioxidant properties; it may serve as a source for the prevention of atherosclerosis and cardiovascular diseases.

Key Words: hypercholesterolemia, atherosclerosis, Artemisia vulgaris extract, TC, TG

Hypercholesterolemia is widely known to be the major risk factor for the development of cardiovascular diseases. It was reported that hypercholesterolemia cause the enhanced production of reactive oxygen species (ROS). Oxidative stress induced by ROS plays an important role in the etiology of atherosclerosis, coronary heart disease. There has been a growing interest in natural products and their role in the maintenance and improvement of health and wellness. The cholesterol-lowering effect of dietary plants has been well studied and various plants were shown to be helpful in lowering plasma cholesterol levels and encouraging safety profile.

Artemisia vulgaris (Mugwort or Common Wormwood Family; Compositae) is one of several species in the genus Artemisia with names containing mugwort. It is native to temperate Europe, Asia and northern Africa, but is also present in North America where it is an invasive weed. In traditional herbal medicine, aerial parts of Artemisia vulgaris are being used as anti-helmint, antiseptic, antispasmodic, a tonic for vital organs and in various disorders including hepatitis.

Kumar and Kumud reported the presence of phenolics, tannins, saponins, alkaloids, phytosterols in mugwort. Another study has identified more than 20 flavonoids in mugwort extracts, as eriodicycl and luteolin. Coumarins, polycyclicenes, sesquiterpene lactones and volatile oil components have previously been reported from mugwort.

In a previous study was conducted by Temraz and El-Tantawy, the authors investigated the antioxidant activity of Artemisia vulgaris extract in vitro by measuring free radical scavenging activity using DPPH. The authors found that the extract exhibited a strong antioxidant activity and also the extract increased the antioxidant levels in normal rats. No studies evaluating the hypolipidemic effects of Artemisia vulgaris extract have been reported so far. Therefore, this study was aimed to determine the hypolipidemic and anti-inflammatory activities of Artemisia vulgaris extract in hypercholesterolemic rats.

Materials and Methods

Chemicals. All chemicals were of analytical grade and purchased from Sigma (St. Louis, MO).

Preparation of the extract. Samples of Artemisia vulgaris were purchased from the Herbarium of the Faculty of Pharmacy, Cairo University, Egypt. The freshly cut plants were dried in the drying room with active ventilation at ambient temperature and packed in paper bags. Dried plants were milled with sample mill (300 Waufn S2, Germany) and approximately (500 g of powder) in turn were extracted with 70% methanol. The extract was evaporated to dryness under vacuum using a rotary. The process of maceration and evaporation was repeated till exhaustion of the plants powder, and then the residues were combined and weighed.

Experimental design. Twenty four male Wistar albino rats weighing (120–140) g were used for this study. The animals were housed in a temperature (25 ± 1°C), humidity controlled room and a 12-h light-dark cycle (lights on at 6:00). Rats were allowed free access to tap water and standard pellet diet. The composition of normal rodent standard pellet and high fat diet (HFD) is shown in Table 1; dietary composition used AIN-76A rodent diet.

The institutional Animal Ethics Committee approved all experimental protocols No. 158 June 2013. The animals were classified into 4 groups, each of 6 as follows: 1) C: rats were kept on standard pellet diet. 2) HFD: rats were kept on HFD containing 3% cholesterol, 9% cotton seed oil, 10% olein oil and 0.5% cholic acid for 8 weeks. 3) HFD + E: rats with HFD were orally administered Artemisia vulgaris extract by stomach tube once daily for a period of 4 weeks. The dose of the extract used in this study was given according to Temraz & El-Tantawy. 4) HFD + Stn: rats with HFD were orally administered Atorvastatin by stomach tube once daily for a period of 4 weeks.

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Assay of serum biochemical parameters. At the end of the experiment, the final body weight for each rat was recorded in each group. Animals were fasted overnight, blood samples were withdrawn from the retro-orbital vein of each animal using a glass capillary tube after fasting period of 6 h. The blood samples were allowed to coagulate and then centrifuged at 3,000 rpm for 20 min. The separated sera were used for the estimation of alanine aminotransferase (ALT) and aspartate transaminase (AST) activities by using commercial kits [Quimica Clinica Aplicada, Amposta (Tarragona), Spain], serum total protein, total cholesterol (TC), triglycerides (TG) and high density lipoprotein (HDL-C). HDL cholesterol is the well-behaved “good cholesterol” removes cholesterol from blood vessels, causing the blockages of atherosclerosis. Higher HDL levels reduce the risk for heart disease, but low levels increase the risk. HDL-C levels were evaluated using kits from Biodiagnostic, Egypt. The method of determination of HDL-C was achieved by precipitation of serum by adding precipitating reagent (phosphotungstic acid and dextran sulfate-magnesium chloride) after centrifugation at 3,000 rpm, the supernatant was estimated for HDL-C by using cholesterol reagent (cholesterol esterase and cholesterol oxidase) and measured colorimetrically at a wavelength of 500 nm. The color intensity is directly proportional to concentration of HDL-C. Low density lipoprotein (LDL-C), is the bad one. LDL collects in the walls of blood vessels, causing the blockages of atherosclerosis. Higher LDL increase risk for a heart attack from a sudden blood clot in an artery narrowed by atherosclerosis was calculated from the equation LDL-C = TC-HDL-C-TG/5.(9) Very low density lipoprotein (VLDL-C) was calculated by dividing TG/5. Atherogenic index (AI) was calculated by the equation: AI = (TC-HDL-C)/HDL-C. Serum urea level was determined using commercial kits purchased from Stanbio (Boeme, TX).

Serum MDA level, end product of lipid peroxidation was estimated by method of Ohkawa et al.(10) NO level was determined by using commercial kit from Biodiagnostica, Cairo, Egypt. TNF-α was estimated in serum by ELISA technique using Uscn, Life Science kit, (11271 Richmond Avenue, Suite H104, Houston, TX 77082). Serum paraoxonase-1 activity was measured as arylesterase with phenyl acetate as substrate according to method described by Fuhrman et al.(10) The initial velocity of phenol formation during the hydrolysis of phenyl acetate was calculated from the increase of absorbance at 270 nm.

Preparation of liver homogenate for estimation of HMG-CoA reductase activity. The livers excised out, washed in ice-cold normal saline, patted dry and weighed. Tissue homogenate (10%) from liver was used for the estimation of HMG-CoA reductase activity according to method described by Rao and Ramakrishnan.(11) HMG-CoA reductase activity is expressed as a ratio of HMG-CoA to mevalonate levels. The ratio of HMG-CoA to mevalonate is inversely proportional to HMG-CoA reductase activity, i.e., an increase in ratio indicates a decrease in activity.

Histopathological study. Aorta was dissected out rapidly, washed with cold saline, and fixed in 10% neutral buffered formalin, dehydrated with 50–100% ethanol solutions, and embedded in paraffin. Four to five micrometer sections were cut and stained with hematoxylin–eosin.

Statistical analysis. Results were shown as mean ± SE for each group. Statistical analysis was performed using SPSS 9.0 for Windows (Chicago, IL). For multiple comparisons, one-way analysis of variance (ANOVA) was used. In cases where ANOVA showed significant differences, Tukey post-tests were performed for multiple group comparison, p<0.05 was considered to be statistically significant.

Results

Effect of Artemisia vulgaris extract on body weight. Administration of HFD resulted in a significant increase in the body weight as compared to their control animals. Treatment of HFD-treated rats with Artemisia vulgaris extract as well as Atorvastatin led to a significant decrease in their body weights when comparing to HFD treated animals, Table 2.

Effect of Artemisia vulgaris extract on serum ALT, AST, total protein and urea. HFD treatment caused a significant increase in serum ALT, AST activities and a significant decrease in total serum protein as compared to their controls. Administration of Artemisia vulgaris extract as well as Atorvastatin to HFD-treated rats revealed a significant decrease in serum ALT, AST activities and a significant increase in total serum protein as compared to HFD. HFD treatment and/or Artemisia vulgaris extract did not alter serum urea, Table 3.

Effect of Artemisia vulgaris extract on serum lipid profile. HFD treatment caused a significant increase in serum TG, TC, LDL-C, VLDL-C level, AI and a significant decrease in the level of HDL-C as compared to controls. Treatment of HFD with

### Table 1. Composition of normal diet and high fat diet (g/kg diet)

| Ingredient       | Normal diet | High fat diet |
|------------------|-------------|---------------|
| Casein           | 250         | 350           |
| Starch           | 460         | 160           |
| Soy bean oil     | 160         | 160           |
| Maltodextrin     | 32          | 30            |
| Cholesterol      | —           | 90            |
| Cotton seed oil  | —           | 100           |
| Olein oil        | —           | 3             |
| L-cystine        | —           | 5             |
| Cellulose        | 50          | 50            |
| Cholic acid      | —           | 10            |
| Mineral mix      | 10          | 12            |
| Vitamin mix      | 35          | 40            |

### Table 2. Body weight in C, HFD, HFD + E and HFD + Stn treated groups

| Group          | Initial body weight (g) | Final body weight (g) |
|----------------|-------------------------|-----------------------|
| C             | 130 ± 3.2               | 161 ± 3.8             |
| HFD           | 129 ± 3.0               | 220 ± 7.7*            |
| HFD + E       | 132 ± 2.8               | 175 ± 5.1*            |
| HFD + Stn     | 133 ± 3.6               | 172 ± 4.3*            |

Results are expressed as mean ± SE. *p<0.05: Significantly different from control group. **p<0.05: Significantly different from HFD treated group.

### Table 3. Serum ALT, AST activities, total protein and urea levels in C, HFD, HFD + E and HFD + Stn treated groups

| Group   | ALT (U/L) | AST (U/L) | Total protein (g/dl) | Urea (mg/dl) |
|---------|-----------|-----------|----------------------|--------------|
| C       | 27.6 ± 0.3| 34.6 ± 0.6| 7.4 ± 0.34           | 33.6 ± 1.7   |
| HFD     | 56 ± 2.7* | 95 ± 3.4* | 6.28 ± 0.2*          | 35.3 ± 1     |
| HFD + E | 28.4 ± 0.4*| 36 ± 0.54*| 7.2 ± 0.21*          | 32.7 ± 1.1   |
| HFD + Stn| 40 ± 1.3* | 53 ± 2.5* | 6.81 ± 0.06*         | 31.7 ± 1.2   |

Results are expressed as mean ± SE. *p<0.05: Significantly different from control group. **p<0.05: Significantly different from HFD treated group. ***p<0.05: Significantly different from HFD + Stn treated group. ALT, alanine transaminase; AST, aspartate transaminase.
Artemisia vulgaris extract as well as Atorvastatin normalized serum lipid profile, Table 4. Also there was a significant increase in LDL-C/HDL-C ratio in HFD as compared to their controls. Treatment of HFD with Artemisia vulgaris extract as well as Atorvastatin significantly decreased LDL-C/HDL-C ratio as compared to HFD, Fig. 1.

Effect of Artemisia vulgaris extract on liver HMG-CoA reductase activity. The hepatic HMG-CoA reductase activity was significantly lowered in the Artemisia vulgaris extract as well as Atorvastatin treated groups than in the HFD model, Fig. 2.

Effect of Artemisia vulgaris extract on serum paraoxonase-1 activity. In HFD model, there was a significant decrease in serum paraoxonase-1 activity when compared to its control value. Administration of Artemisia vulgaris extract as well as Atorvastatin to HFD, significantly increased the enzyme activity in relation to HFD, Fig. 3.

Effect of Artemisia vulgaris extract on serum TNF-α level. HFD treatment caused a significant increase in serum TNF-α level when compared to its control value. Administration of Artemisia vulgaris extract to HFD, significantly decreased the level of serum TNF-α when compared to HFD, Fig. 4.

Table 4. Serum lipid profile in C, HFD, HFD + E and HFD + Stn treated groups

| Group   | TG (mg/dl) | TC (mg/dl) | HDL-C (mg/dl) | LDL-C (mg/dl) | VLDL-C (mg/dl) | AI          |
|---------|------------|------------|---------------|---------------|---------------|-------------|
| C       | 61 ± 3.6   | 76 ± 2.1   | 29.8 ± 2.9    | 41 ± 1.4      | 12.2 ± 0.7    | 1.98 ± 0.18 |
| HFD     | 93 ± 4.6a  | 124 ± 6.4a | 21.5 ± 0.6a   | 89 ± 3.5a     | 18.7 ± 0.93a  | 4.8 ± 0.2a  |
| HFD + E | 59.3 ± 1.4a| 72.2 ± 1b  | 28.1 ± 2.2a   | 39 ± 1.1a     | 11.8 ± 0.3a   | 2 ± 0.26a   |
| HFD + Stn| 58 ± 2.6a  | 78 ± 4.9a  | 29 ± 2.4a     | 40 ± 1.5a     | 11.5 ± 0.5a   | 2.1 ± 0.22a |

Results are expressed as mean ± SE. *p<0.05: Significantly different from control group, bp<0.05: Significantly different from HFD treated group.

Fig. 1. Effect of Artemisia vulgaris extract on serum LDL-C/HDL-C in C, HFD, HFD + E and HFD + Stn treated groups. Values are expressed as mean ± SEM, n = 6. *p<0.05: significantly different from control group, bp<0.05: significantly different from HFD treated group.

Fig. 2. Effect of Artemisia vulgaris extract on liver HMG-CoA reductase activity in C, HFD, HFD + E and HFD + Stn treated groups. Values are expressed as mean ± SEM, n = 6. *p<0.05: significantly different from control group, bp<0.05: significantly different from HFD treated group.

Fig. 3. Effect of Artemisia vulgaris extract on serum paraoxonase-1 activity in C, HFD, HFD + E and HFD + Stn treated groups. Values are expressed as mean ± SEM, n = 6. *p<0.05: significantly different from control group, bp<0.05: significantly different from HFD treated group.

Fig. 4. Effect of Artemisia vulgaris extract on serum TNF-α level in C, HFD, HFD + E and HFD + Stn treated groups. Values are expressed as mean ± SEM, n = 6. *p<0.05: significantly different from control group, bp<0.05: significantly different from HFD treated group, cp<0.05: significantly different from HFD + E group.
Effect of *Artemisia vulgaris* extract on serum MDA and NO level. HFD treatment caused a significant increase in serum MDA and NO level when compared to their control levels. Treatment with *Artemisia vulgaris* extract as well as Atorvastatin, significantly decreased the levels of serum MDA and NO when compared to HFD, Fig. 5 and 6.

**Histopathological investigation of aorta.** In control rats, there was no histopathological alteration and the normal histological structure of the endothelium of the intima, and the underlying media then the adventitia were recorded in Fig. 7A. In HFD-treated rats, desquamation was noticed in the endothelium of the intima while the media showed vacuolar degeneration and the underlying adventitia had inflammatory cells infiltration. Fig. 7B. Treatment of HFD-treated rats with *Artemisia vulgaris* extract (C): the adventitia showed mild inflammatory cells infiltration & HFD-treated rat + 10 mg/kg Atorvastatin (D): mild vacuolar degeneration in the media and the adventitia showed inflammatory cells infiltration, arrows indicate the lesions.
Atorvastatin, there was mild vacuolar degeneration in the media and the adventitia showed inflammatory cells infiltration, Fig. 7D.

Discussion

The present study revealed that feeding of rats with HFD for 8 weeks resulted in significant increase in plasma TC, TG and LDL-C accompanied with significant decrease in HDL-C level. It has been shown by other investigators that an increase in dietary cholesterol intake in animals led to hypercholesterolemia.\(^{12,13}\)

Nabel reported that the elevated plasma levels of LDL-C are attributed to impairing the activity of hepatic LDL receptors, which normally clear LDL from the plasma.\(^{14}\)

Several authors have suggested that peroxidative modification of LDL is an important factor in atherosclerotic changes.\(^{15–17}\) Oxidative modification of LDL alters its structure allowing LDL to be taken up by scavenger receptors on macrophage, endothelial and smooth muscle cells, leading to the formation of lipid-laden foam cells, the hallmark of early atherosclerotic lesions.\(^{18}\)

In the present work, administration of *Artemisia vulgaris* extract provides a beneficial action on lipid metabolism with regard to the reduction of AI. The AI was deceased after *Artemisia vulgaris* extract treatment in HFD treated rats. This ameliorative action was due to the plasma lipid-lowering activity of the extract. *Artemisia vulgaris* extract significantly suppressed the higher values of LDL-C/HDL-C ratio in HFD-treated rats and could inhibit the progression of atherosclerosis as supported by histopathological study, Fig. 7C; this might be partly attributable to its hypocholesterolemic property.

In the current study, hypocholesterolemic activity of the extract could be attributed to its inhibition of hepatic HMG-CoA reductase activity (HMG-CoA reductase is a key rate limiting enzyme involved in the cholesterol biosynthetic pathway) in such manner the extract may exert its hypocholesterolemic effect through the mechanism of Atorvastatin (standard drug used in this study).

Phytochemical analysis of *Artemisia vulgaris* extract revealed the presence of tannins, flavonoids, steroidal saponins, alkaloids, phenolics, and steroids.\(^{19}\) Flavonoids and polyphenols may also contribute to the hypolipidemic activity by increasing the cholesterol metabolism and by modulating the enzymes involved in cholesterol metabolism, such as HMG-CoA reductase, lecithin cholesterol acyltransferase, cholesterol 7α-hydroxylase and acyl-CoA:cholesterol acyltransferase.\(^{20,21}\) Also, it has been reported that flavonoids intake decreased LDL-C and increased HDL-C that may hasten removal of cholesterol from peripheral tissue to liver for catabolism and excretion.\(^{22,23}\)

In a previous work by Wang et al.,\(^{22}\) the hypolipidemic effect of steroidal saponin (trillin) has been investigated in rats fed with high fat diet. The author reported that the intra-peritoneal administration of trillin into those rats significantly improved the lipid profile and the treatment restored the levels of TC, TG, LDL and HDL back to the normal condition.

Steroidal saponins are known to elicit serum cholesterol lowering activity by causing resin-like action, thereby reducing the enterohepatic circulation of bile acids and they are reported to increase fecal cholesterol excretion.\(^{23}\) It has been reported that steroidal saponins possess hypolipidemic activity through increase the lipoprotein lipase activity, which helps to remove free fatty acids from circulation, causing decrease in cholesterol level. Also, steroidal saponins decreased cholesterol absorption and increased biliary cholesterol secretion, thereby producing hypolipidemic condition.\(^{24}\)

Hyperlipidemia increases superoxide formation which is responsible for increasing peroxynitrite that resulted from the reaction of singlet oxygen (O\(_2\)\(^{\ast}\)) and NO radical. \(^{25}\) Also, increased caloric intake is an important factor in decreasing the mitochondrial membrane fluidity and increasing the generation of ROS and reactive nitrogen species.\(^{26}\)

The results of the present study indicated that there was a significant decrease in serum level of MDA and NO in HFD treated by *Artemisia vulgaris* extract as compared to HFD. The antioxidant activity of *Artemisia vulgaris* extract could be attributed to its flavonoidal content. Flavonoids act as scavengers of various oxidizing species i.e., super oxide anion (O\(_2\)\(^{\ast}\)), hydroxyl radical or peroxy radicals, they also act as quenchers of singlet oxygen.\(^{27}\) Also the antioxidant activity of *Artemisia vulgaris* extract could be attributed to the presence of tannins. Tannins are stronger in their antioxidant and anti-radical activities because tannins possess more numbers of hydroxyl groups than flavonoids.\(^{28}\)

There is a highly positive relationship between total phenolics and antioxidant activity of many plant species, because of the scavenging ability of their hydroxyl groups. It was also reported that phenolic compounds are effective hydrogen donors, making them very good antioxidants.\(^{29}\)

Paraoxonase-1, the lipophilic antioxidant component of HDL-C has been shown to reduce the susceptibility of LDL to lipid peroxidation. Paraoxonase-1, with its antioxidant activity, protects lipoproteins against oxidation, probably by hydrolyzing specific lipid peroxides. Its serum concentration is influenced by inflammatory changes and the levels of serum oxidised-LDL.\(^{30}\)

In the present work, there was a significant decrease in serum paraoxonase-1 activity in HFD as compared to control rats. These results in agreement with that of El-Beshbishy et al.\(^{31}\) the author reported a decrease in serum paraoxonase-1 activity in hyperlipidemic rats. Treatment of HFD by *Artemisia vulgaris* extract significantly increased paraoxonase-1 activity as compared to HFD. Luteolin is one of the identified flavones in *Artemisia vulgaris* extract has been reported to induce paraoxonase-1 activity,\(^{32}\) this may explain the increase in paraoxonase-1 activity upon the administration of the extract.

Atherosclerosis is an inflammatory disease and does not result simply from the accumulation of lipids. Cytokines play an important role in atherosclerosis. Recruitment of circulating cytokines like TNF-α and interleukin-1α (IL-1α) into vessel wall is crucial for the initiation and progression of atherosclerotic lesion.\(^{33,34}\)

In the present work, there was a significant increase in serum level of TNF-α in HFD as compared to control rats. These results in agreement with that of Margoni et al.\(^{35}\) The author stated an increase in serum TNF-α level in hyperlipidemic rats. Treatment with *Artemisia vulgaris* extract significantly reduced the elevated levels of serum TNF-α in HFD animals. According to Ahmadiani et al.,\(^{36}\) the anti-inflammatory effect of the *Artemisia vulgaris* extract may be due to the presence of flavonoids, tannins, alkaloid, and saponins.

In conclusion, the *Artemisia vulgaris* extract has hypolipidemic, anti-inflammatory, antioxidant properties. The hypolipidemic effect is attributed to the HMG-CoA reductase inhibiting effect of extract. Based on the results of our study, it can be suggested that *Artemisia vulgaris* extract has high therapeutic potential and it may serve as a source for the prevention of atherosclerosis and cardiovascular diseases. The declined oxidative stress can be due to the improved antioxidant status by extract. The exhibited biological activities can be explained with the properties of polyphenols and saponins present in the *Artemisia vulgaris* extract.

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Abbreviations

- AI: atherogenic index
- ALT: alanine transaminase
- AST: aspartate transaminase
- HDL-C: high density lipoprotein
- HFD: high fat diet
- HMG-CoA reductase: 3-hydroxy-3-methylglutaryl coenzyme-A reductase
- LDL-C: low density lipoprotein
- MDA: malondialdehyde
- NO: nitric oxide
- ROS: reactive oxygen species
- TC: total cholesterol
- TG: triglycerides
- TNF-α: tumor necrosis factor-α
- VLDL-C: very low density lipoprotein

Conflicts of Interest

No potential conflicts of interest were disclosed.

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