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# Antihyperglycemic and Antihyperlipidemic Effects of Hydroalcoholic Extract of *Ferulago angulta* in Experimental Hyperlipidemic Rats

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## Abstract

**BACKGROUND:** Metabolic disorders, and their consequences, are among the most important hygienic problems of modern life.

**OBJECTIVES:** Due to the increased global interest in natural remedies and their importance in the treatment of diseases, *Ferulago angulata,* as one of the oldest known medicinal plants of folk medicine, was evaluated its hypolipidemic and hypoglycemic effects.

**METHODS:** A total of 147 adult male rats were randomly divided into seven groups, each with three replicates (n=7): control group, untreated hyperlipidemia group, three treated hyperlipidemia groups, treated with 125, 250, and 500 mg/kg of the *F. angulata* hydroalcoholic extract (FAHE), two hyperlipidemia groups treated with atorvastatin (10 mg/kg), and metformin (500 mg/kg). After 21 days, serum glucose and total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein (VLDL), and the ratios of LDL/HDL and TC/LDL, were measured.

**RESULTS:** In all hyperlipidemia groups treated with different doses of FAHE, glucose, TG, TC, LDL-C, and LDL/HDL ratios were significantly reduced, while significant increases in HDL-C and cholesterol/LDL ratios were observed compared to the untreated hyperlipidemia group; however, a significant reduction of VLDL was only observed at the dose of 500 mg/kg FAHE. Hypolipidemic and hypoglycemic effects of FAHE at 250 and 500 mg/kg doses were comparable to atorvastatin and metformin.

**CONCLUSIONS:** These results indicated the hypolipidemic and hypoglycemic effects of FAHE, which may be due to the high phenolic, flavonoids, and trace element contents, providing powerful antioxidant potential and affecting the enzymatic pathways of lipid and glucose synthesis and metabolism.

**KEYWORDS:** Atorvastatin, *Ferulago angulata*, Hyperglycemia, Hyperlipidemia, Metformin

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## Introduction

Hyperlipidemia is defined as high levels of fasting total cholesterol (TC) and/or high blood levels of triglyceride (TG)-carrying lipoproteins (Nelson, 2013). High levels of low-

density lipoprotein (LDL), along with low levels of high-density lipoprotein (HDL), lead to the buildup and development of lipid plaques on the arterial endothelial surface, which is a predisposing factor for atherosclerosis and related diseases (Hao & Friedman, 2014; Nelson, 2013). Meta-analysis studies have been revealed that in Iran, the prevalence of hypercholesterolemia is significantly higher than the global average (Tabatabaei-Malazy *et al*., 2014).

Hyperlipidemia is a consequence of nutritional and lifestyle factors (such as obesity and high cholesterol intake) and some diseases (such as diabetes); it is associated with increased incidence and consequences of type 2 diabetes (Chen *et al*., 2015; Onwe *et al*., 2015). Type 2 diabetes is principally the outcome of obesity and inadequate physical activity, involving about 6% of the world's population and 90% of the diabetes patients (Ruel *et al*., 2006).

Atorvastatin is universally recommended for the medical care of hyperlipidemia. It decreases cholesterol synthesis via competitive inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme of the mevalonate pathway, which produces cholesterol and other isoprenoids, increases the cholesterol uptake by hepatocytes through upregulation of LDL receptor expression, and reinforces catabolism of plasma LDL (Golomb *et al*., 2008; Ramachandran & Wierzbicki, 2017).

Metformin has been considered the drug of choice for the treatment of type 2 diabetes, especially in obese people (Kong *et al*., 2012). It decreases hepatic gluconeogenesis via glucagon antagonism, inhibition of the mitochondrial respiratory chain and glycerophosphate dehydrogenase, insulin-sensitizing effect to enhance peripheral glucose uptake, and decreasing glucose absorption from the Gastrointestinal tract (GIT) (Rena *et al*., 2013; Vos *et al*., 2016). Due to the considerable side effects of the chemical hypolipidemic and hypoglycemic drugs (e.g., memory loss, neuro-pathy, pancreatitis, hepatotoxicity, diabetes mellitus, myopathy, GIT irritation, and, more seriously, lactic acidosis), a strong tendency toward natural remedies with fewer side effects has been increased (Golomb *et al*., 2008; Rouhi-Boroujeni *et al*., 2015; Toth *et al*., 2018; Vos *et al*., 2016).

*Ferulago angulata* (Chavil in Persian), a perennial plant of the Apiaceae family, grows predominantly in the mountains of Iran, Turkey, and Iraq and possesses numerous traditional and modern applications, such as aphrodisiac, sedative, tonic, digestive, air freshener, flavoring agent, antimicrobial, anticancer, and antidiabetic effects (Aghaei *et al*., 2014, Kiziltas *et al*., 2017).

The *F. angulata* extract has a significant antioxidant effect due to the rich source of phenolic compounds (Azarbani *et al*., 2014). Since phenolic compounds are effective on lipid and glucose metabolism (Aqeel, 2018), this study was designed to investigate the hypolipidemic and hypoglycemic effects of the *F. angulata* hydroalcoholic extract (FAHE) on experimental hyperlipidemic rats.

## Materials and Methods

### Preparation of the *F. Angulata* Hydroalcoholic Extract

*F. angulata* was collected from Ilam Mountains, Ilam Province, west of Iran, and approved by the Agricultural and Natural Resources Research center and Agriculture College of Ilam University. After cleaning, the aerial parts were dried in shadow, ground into powder, packed (150 g) into a filter paper, and placed in a Soxhlet apparatus (PecoFood PSU-500, Iran) containing 1000 mL of ethanol (Merck, Germany)/water (80/20, v/v) as a solvent for 12–18 h. Then, the crude extract was concentrated using a rotary evaporator (N-1100, EYELA,

Japan), transferred into a sterile bottle, and subsequently oven-dried at 40°C for 24 h (Mohsenipour & Hassanshahian, 2015).

**Animals**

A total number of 147 male adult Sprague-Dawley rats (Pasteur Institute, Tehran, Iran) weighing 150±220 g were purchased and kept under standard laboratory conditions in accordance with the European Community Guidelines for the care and use of laboratory animals (22°C±1°C ambient temperature, 12 h dark/light cycle, and 55%–56% relative humidity) in standard cages with free access to pellets and fresh water. The study was approved by the University Research Ethics Committee (97GRN1M1904). After one week of acclimatization, animals were randomly divided into seven groups (n=7), each with three replicates (Montero-Bullon *et al*., 2019).

**Hypolipidemic and Hypoglycemic Activity Assessment**

A high cholesterol diet was prepared by dissolving 2 g cholesterol (Sigma-Aldrich, USA) in 50 mL of warm olive oil (Sabroso, Spain) and then thoroughly mixed with 1 kg of a standard pellet diet. The experimental schedule is shown in Table 1. All medications in the treatment groups were administered once a day orally using the gavage method for 21 days (Cheraghi *et al*., 2016; Ye *et al*., 2018).

**Table 1.** Treatment procedure of the experiments

| Group | Diet | Treatment |
|---|---|---|
| **1** | Standard chow pellet | - |
| **2** | High cholesterol diet | - |
| **3** | High cholesterol diet | 125mg/kg FAHE |
| **4** | High cholesterol diet | 250mg/kg FAHE |
| **5** | High cholesterol diet | 500mg/kg FAHE |
| **6** | High cholesterol diet | 10mg/kg Atorvastatin (Pfizer's, USA) |

**Biochemical Analysis**

On the 21st day, rats were anesthetized with ether, and blood samples were collected from cardiac puncture, left at room temperature for 15 min, and centrifuged at 2500 rpm for 15 min (Cheraghi *et al*., 2016). Sera were analyzed for biochemical parameters, including serum glucose, TC, TG, HDL-C, and LDL-C, using commercial kits (Pars Azmoon Kits, Tehran, Iran), and, on this basis, LDL/HDL and TC/LDL ratios were also calculated

**Statistical Analysis**

Data were expressed as mean±SD and evaluated by one-way analysis of variance (ANOVA), followed by Tukey's multiple comparisons using SPSS 11.5 (SPSS Inc., Chicago, Ill., USA) ($P$<0.05).

## Results

**Total Cholesterol**

Experimental hyperlipidemia was approved by a significant increase in lipid profile parameters, including TG, LDL, very low-density lipoprotein (VLDL), TC, and TC/LDL, compared to the normal diet ($P$<0.05). Administration of 125, 250, and 500 mg/kg of FAHE significantly decreased TC compared to the untreated high cholesterol diet ($P$<0.05), which at 250 and 500 mg/kg, it was significantly more notable than atorvastatin ($P$<0.05). Further, there was no significant difference between 250 and 500 mg/kg FAHE ($P$>0.05; Figure 1A).

**Low-Density Lipoprotein Cholesterol**

In all treatment groups, the LDL level significantly decreased ($P$<0.05), so that, at 250 and 500 mg/kg FAHE, it was even significantly lower than a normal diet ($P$<0.05). Further,

there was no significant difference neither between 250 and 500 mg/kg FAHE nor between atorvastatin and FAHE 125 mg/kg ($P$>0.05; Figure 1B).

**High-Density Lipoprotein Cholesterol**

There was not any significant difference in the HDL-C level between normal and untreated high cholesterol diets ($P$<0.05), but atorvastatin and all doses of FAHE significantly increased HDL-C ($P$<0.05). No significant difference was seen between atorvastatin and 125 and 250 mg/kg doses of FAHE ($P$>0.05); however, 500 mg/kg FAHE increased HDL-C significantly more than other groups ($P$<0.05; Figure 1C).

**Very Low-Density Lipoprotein**

Atorvastatin significantly decreased VLDL compared to FAHE and even normal diet ($P$<0.05), but in the FAHE treatment groups, a significant decrease was only seen in 500 mg/kg FAHE ($P$<0.05; Figure 1D).

**Triglyceride**

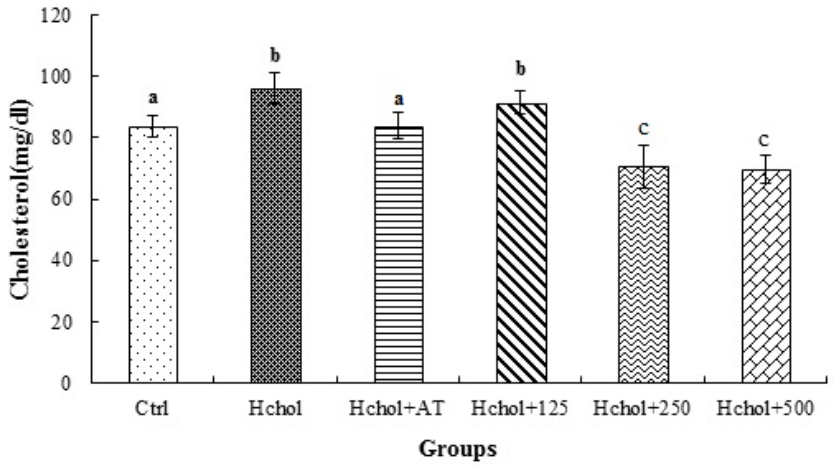
Administration of atorvastatin and 125, 250, and 500 mg/kg FAHE significantly decreased total TG compared to the high cholesterol untreated group ($P$<0.05). However, there was no significant difference between 125, 250, and 500 mg/kg doses of FAHE and normal diet ($P$>0.05). Atorvastatin decreased the TG level significantly more than other groups ($P$<0.05; Figure 1E).

**Low-density Lipoprotein Cholesterol/High-Density Lipoprotein Cholesterol Ratio**

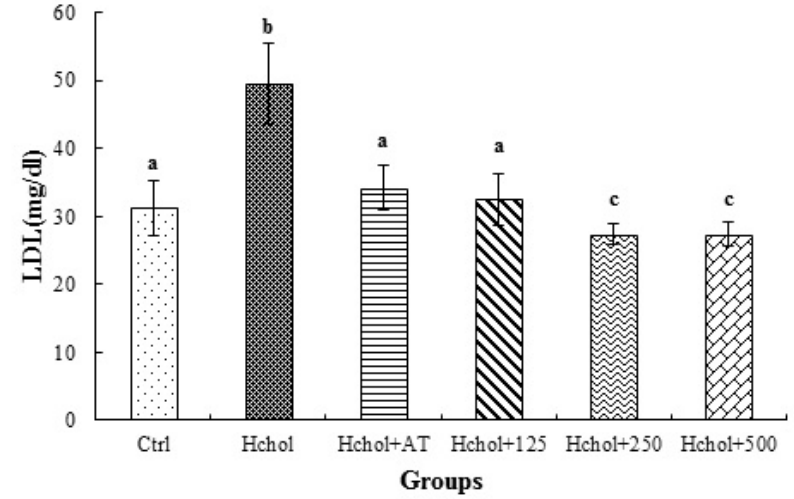
Atorvastatin and FAHE significantly increased HDL-C in parallel with a decrease in LDL-C, so the LDL/HLD ratio significantly decreased ($P$<0.05). There was no significant difference between the normal diet, atorvastatin, and 125 mg/kg FAHE ($P$>0.05), but 250 and 500 mg/kg FAHE decreased the LDL/HDL ratio significantly more than other groups ($P$<0.05; Figure 2A).

**Cholesterol/Low-Density Lipoprotein Cholesterol Ratio**

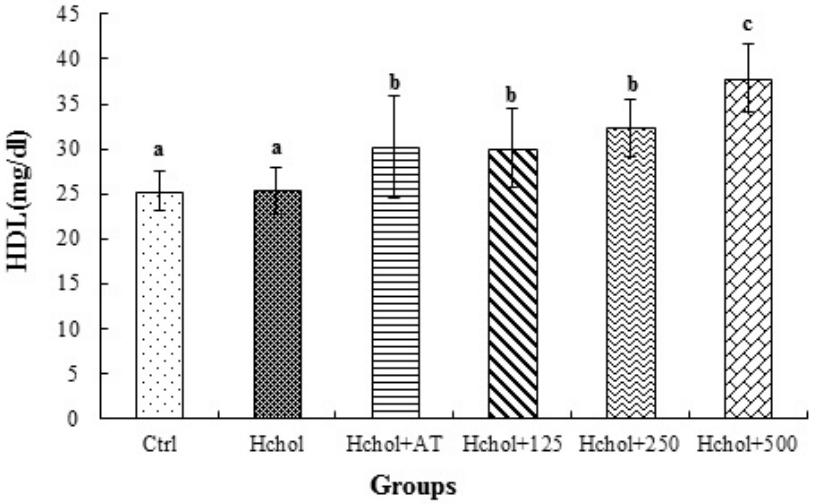
Administration of atorvastatin and FAHE significantly decreased both TC and LDL, so that the TC/LDL ratio significantly decreased ($P$<0.05) in the high cholesterol diet groups than in the high cholesterol untreated group (Figure 2B).



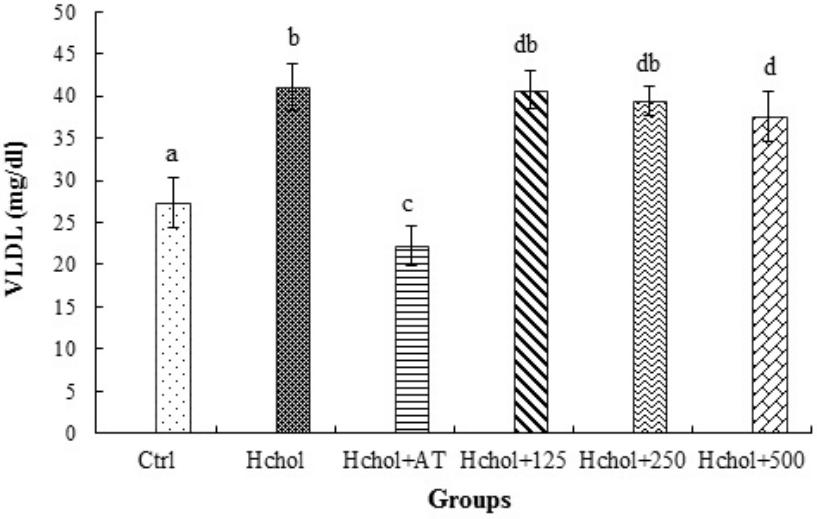

A


LDL(mg/dl)
60
50
40
30
20
10
0
a
b
a
a
c
c
Ctrl
Hchol
Hchol+AT
Hchol+125
Hchol+250
Hchol+500
Groups

**B**


HDL(mg/dl)
45
40
35
30
25
20
15
10
5
0
a
a
b
b
b
c
Ctrl
Hchol
Hchol+AT
Hchol+125
Hchol+250
Hchol+500
Groups

**C**


VLDL (mg/dl)
50
45
40
35
30
25
20
15
10
5
0
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db
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d
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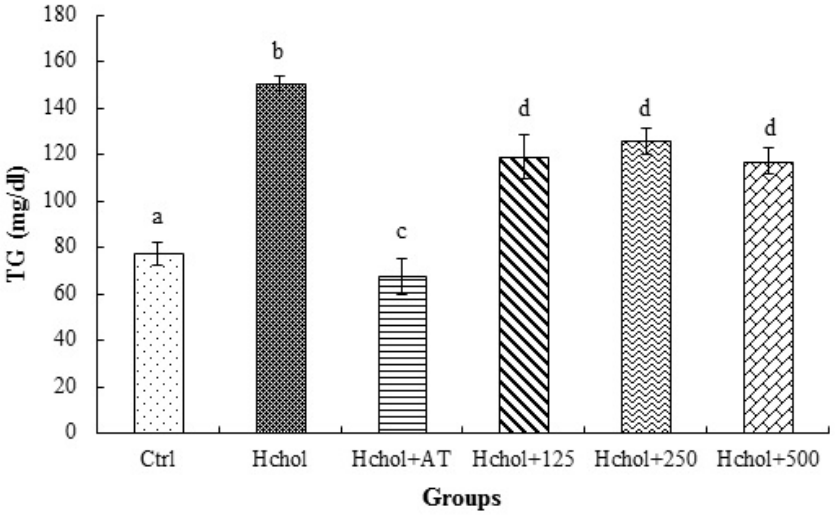
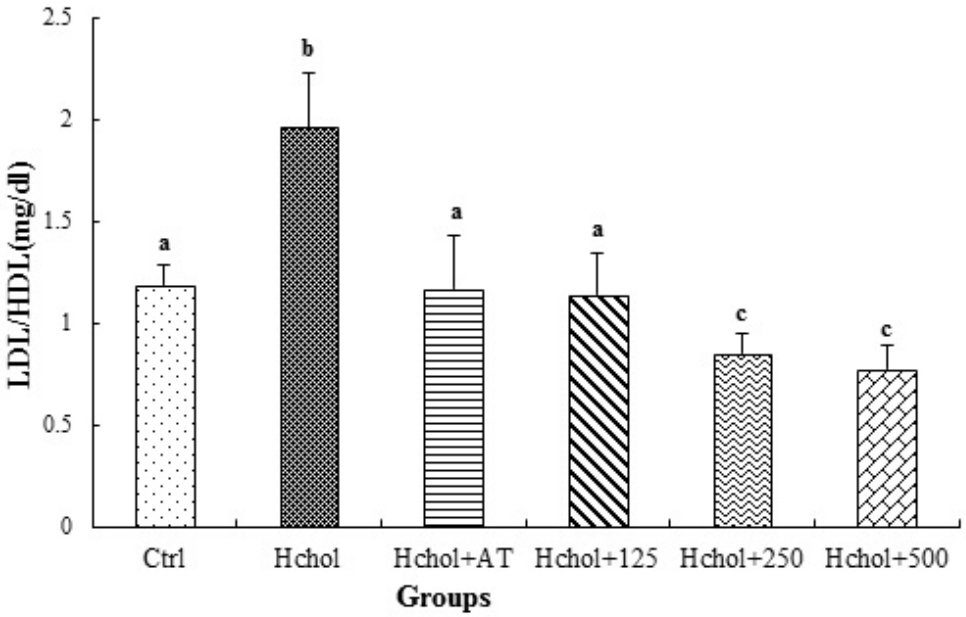
Hchol
Hchol+AT
Hchol+125
Hchol+250
Hchol+500
Groups

**D**

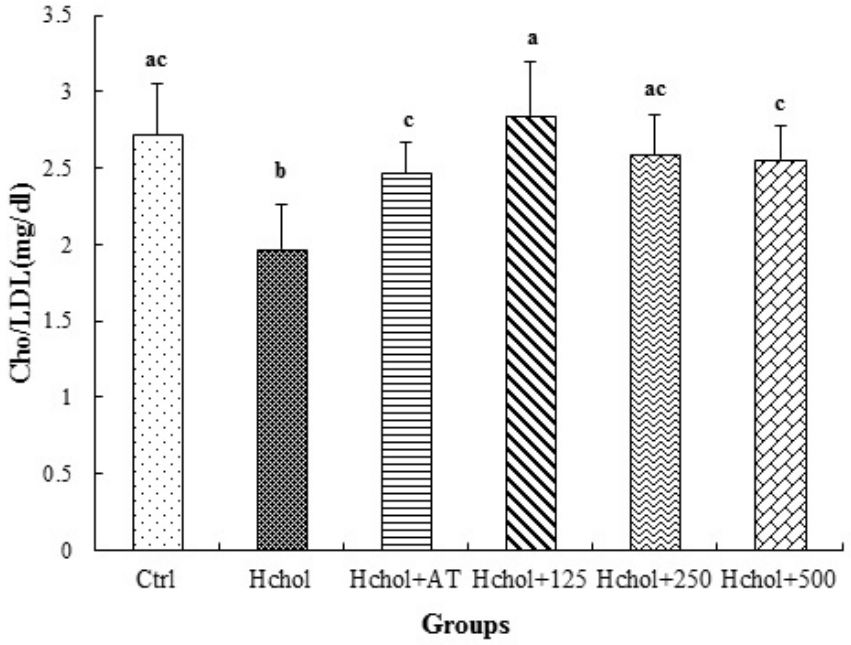



**E**

**Figure 1.** Effects of FAHE and atorvastatin on serum levels of (A) Cholesterol, (B) LDL-C, (C) HDL-C, (D) VLDL, (E) and TG in rats fed on high- cholesterol diet. Abbreviations: Ctrl, control normal control diet group; Hchol, high-cholesterol diet untreated group; Hchol+AT; high-cholesterol diet plus Atorvastatin; Hchol+125, Hchol+250 and Hchol+500, high-cholesterol diet plus 125, 250 and 500 mg/kg of FAHE respectively. Data are expressed as mean ±s standard deviation and different superscript letters show significant differences ($P$<0.05) between groups.




A




B

**Figure 2.** Effects of FAHE and atorvastatin on serum levels of (A) LDL/HDL ratio and (B) Cho/LDL ratio in rats fed on high- cholesterol diet. Abbreviations: Ctrl, control normal control diet group; Hchol, high-cholesterol diet untreated group; Hchol+AT; high-cholesterol diet plus Atorvastatin; Hchol+125, Hchol+250 and Hchol+500, high-cholesterol diet plus 125, 250 and 500 mg/kg of FAHE respectively. Data are expressed as mean ±s standard deviation and different superscript letters show significant differences ($P$<0.05) between groups.

**Glucose**

Experimental hyperlipidemia significantly increased the glucose level ($P$<0.05), which was significantly decreased by FAHE dose dependently ($P$<0.05). There was no significant difference between metformin and 250 mg/kg FAHE ($P$>0.05), but 500 mg/kg FAHE decreased the glucose level significantly more than metformin ($P$>0.05; Figure 3).

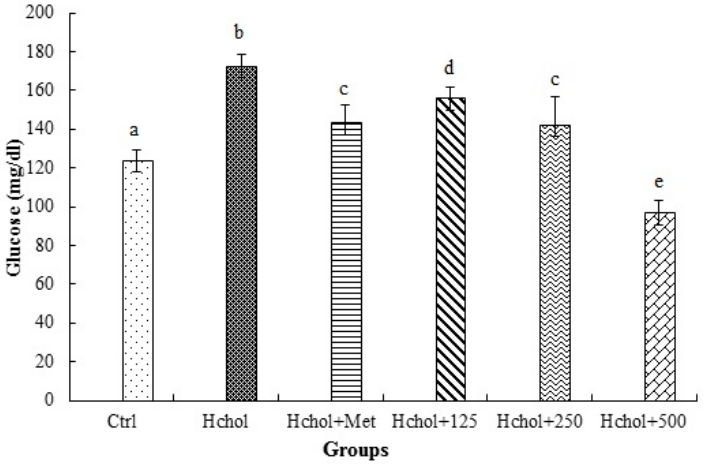



**Figure 3.** Effects of FAHE and atorvastatin on serum levels of glucose in rats fed on high- cholesterol diet. Abbreviations: Ctrl, control normal control diet group; Hchol, high-cholesterol diet untreated group; Hchol+Met; high-cholesterol diet plus Metformin; Hchol+125, Hchol+250 and Hchol+500, high-cholesterol diet plus 125, 250 and 500 mg/kg of FAHE respectively. Data are expressed as mean ±s standard deviation and different superscript letters show significant differences ($P$<0.05) between groups.

## Discussion

High cholesterol diet increased free fatty acids, that is a predisposing risk factor for type 2 diabetes increasing cellular response and sensitivity to insulin; therefore, it is used as an experimental method for induction of diabetes type 2 (Chen *et al*., 2015; Matos *et al*., 2005). In this study, experimental hypercholesterolemia increased lipid profile, but FAHE significantly decreased TC, TG, LDL, and LDL/HDL ratio due to the increased HLD level. For VLDL, this decline was only significant at 500 mg/kg; surprisingly, the hypolipidemic effects of 250 and 500 mg/kg FAHE on LDL-C and TC were significantly greater than atorvastatin.

The elevated level of lipid profile in cholesterol-supplemented diets has been previously reported (Ghasempour *et al*., 2007; Wang *et al*., 2010). The prominent antihyperlipidemic effects of some flavonoid-rich plants, such as *Kelussia odoratissima*, *Zataria multiflora, Cynara scholium's*, *Cynara scolymus,* and Cranberry, have been reported (Elrokh *et al*., 2010; Nazni *et al*., 2006; Ruel *et al*., 2006; Samarghandian *et al*., 2016; Sarian *et al*., 2017). The lipid-lowering effect of FAHE may be related to the flavonoid contents, which seems to exert atorvastatin-like effects on the suppressing hepatic production of the major apolipoprotein B100 (apoB100) lipoproteins, enhancing LDL receptor gene expression and increasing lipoprotein clearance; also, plant fibers may inhibit cholesterol absorption parallel with increasing its excretion (Pal *et al*., 2003).

Flavonoids decrease cholesterol and LDL-C formation by increasing unsaturated fatty acids and chylomicron clearance (Frota *et al*., 2010). Flavonoids inhibit hydroxymethylglutaryl-CoA (HMG-CoA), which is the rate-limiting enzyme in the mevalonate synthesis pathway, thus decreasing cholesterol formation. They inhibit lipid peroxidation, act as hydroxyl and peroxide free radical scavengers, and activate lipoprotein lipase to catalyze the hydrolysis of the TG content of chylomicrons and VLDL. Polyphenolic compounds (e.g., flavonoids) decline postprandial intestinal chylomicron formation and absorption, decreasing the TG level. Moreover, they exert anti-obesity effects due to the prevention of TG accumulation in adipocytes (Elrokh *et al*., 2010).

Different constituents have been identified in the essential oil of *F. angulata* aerial parts, in which most of them exhibited significant antioxidant activity (Ghasempour *et al*., 2007; Hosseini *et al*., 2012). γ-Terpinene is a component of *F. angulata* seeds, indicating antihyperlipidemic effects via stimulatory effects on lipoprotein lipase activity and peroxisomal fatty acid beta-oxidation (Takahashi *et al*., 2003). Also, the hypocholesterolemic effect of other components of *F. angulata* extracts (e.g., thymol and carvacrol) has been shown by inhibiting the HMG-CoA reductase. Carvacrol stimulates lactobacillus probiotics, which decreases lipid profile, especially cholesterol, via cholesterol attachment to the probiotic wall, transforms the cholesterol to coprostanol, and finally increases fecal cholesterol excretion (Ghasemi-Pirbalouti *et al*., 2016; Lee *et al*., 2003).

The overproduction of free radicals increases the risk of hyperlipidemia; therefore, polyphenols are recognized as anti-hyperlipidemic compounds with free radical scavenging activity (Harnafi *et al*., 2008; Yang *et al*., 2008). Thus, it seems that the hypolipidemic effects of FAHE may be in part due to the polyphenolic content and antioxidant properties, which decreases free radicals induced oxidative damages. The *F. angulata* extract contains 90±4.11 of total phenolic (mg GA/g), and 37.39±2.85 total flavonoid (mg QE/g) content, which induce 51.58±5.65%, 68.67±139%,

34.37±12.28%, and 70.82±0.76% for oxygen, hydroxyl, $H_2O_2$, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical inhibition percentage. Notably, the free radical scavenging activity of the *F. angulata* extract against $H_2O_2$ was comparable to Butylated hydroxytoluene (BTH), and, for DPPH, it was even more than BTH. Additionally, the plant extract showed suitable stimulatory effects on hepatic antioxidant enzymes, such as Catalase (CAT), Superoxide dismutase (SOD), and Glutathion peroxidase (GSH-Px) (Kizitas *et al*., 2017).

The antioxidant effect of *F. angulata* may contribute to its hypolipidemic properties by preventing the oxidative modification of LDL-C (Rafieian-Kopaei *et al*., 2014; Rouhi-Boroujeni *et al*., 2015). Furthermore, other antioxidants, such as vitamins A, C, and E, were found in high amounts in the metabolic extract of *F. angulata* (Kizitas *et al*., 2017). It is well determined that vitamin E exhibited hypolipidemic action by regulating gene expression involved in the lipid metabolism and peroxisome proliferator-activated receptor gamma (PPAR-$\gamma$) transduction pathway (Aghadavoud *et al*., 2018). Ascorbic acid facilitates the conversion of hepatic cholesterol to bile acids and thereby reduces serum cholesterol, as well as protects HDL from oxidative modification (Ginter *et al*., 1982; Hillstrom *et al*., 2003).

A significant increase in the HDL-C level of the FAHE groups may be due to the presence of flavonoid contents. Herbal flavonoids increase HDL production by activating lipid trans-porters, such as ATP-binding cassette transporter (ABCA1), affecting apoA1 concentration and increasing hepatic paraoxonase 1 expression (Millar *et al*., 2017). Increasing HDL-C levels by statins may be due to inhibition of cholesteryl ester transfer protein (CETP), which promotes the removal of CE from HDL (Barter *et al*., 2010).

Current studies show that cardiovascular risk can be increased due to the relatively high levels of the LDL/HDL ratio, probably by the function of LDL in delivering cholesterol to cells and the role of HDL in cholesterol transport from cells to the liver (Kamesh & Somathi, 2012). Our findings proved that FAHE markedly decreases in the LDL/HDL ratio, which can be caused by decreasing the plasma TC level.

hypoglycemic effect of500 mg/kg FAHE was obvious and more prominent than other groups. Flavonoids present in FAHE may act as the potent α-glucosidase and α-amylase inhibitor, which retards glucose absorption from the digestive tract and inhibits dipeptidyl peptidase IV (DPP-ٔ), increasing plasma insulin levels (Sarian *et al*. 2017).

## Conclusion

FAHE exhibited considerable hypolipidemic and hypoglycemic effects in the experimental hyperlipidemic rats, which may be due to the presence of the rich source of polyphenolic compounds, flavonoids, and trace elements.

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## Conflict of Interest

The authors of the manuscript declared they have no conflict of interest.

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# بررسی اثرات کاهش‌دهندۀ لیپید و قند خون عصارۀ هیدروالکلی گیاه چویل در موش‌های صحرایی هیپرلیپیدمیک

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**زمینه مطالعه:** اختلالات متابولیکی از قبیل هیپرلیپیدمی، دیابت و عوارض ناشی از آنها از مهمترین مشکلات بهداشتی زندگی مدرن است.

**هدف:** به دلیل نقش مهم و افزایش اقبال عمومی به روش‌های درمانی طبیعی بیماری‌ها، در این مطالعه، از گیاه دارویی چویل (*Ferulaga angulate*) که یکی از قدیمی‌ترین و شناخته‌شده‌ترین گیاهان دارویی است، استفاده شده است. در طب سنتی از این گیاه استفاده می‌شود که دارای اثرات پایین‌آورندۀ چربی و قند خون است.

**روش کار:** ۱۴۷ سر موش صحرایی نر به ۷ گروه ۷تایی و سه تکرار شاکل، گروه‌های کنترل، گروه جیره پرچرب، گروه‌های با جیرۀ پرچرب و به ترتیب مقادیر mg/kg ۵۰۰، ۲۵۰ ، ۱۲۵عصارۀ گیاه چویل، آتورواستاتین(mg/kg ۱۰) و متفورمین ( mg/kg۵۰۰). پس از ۲۱ روز مقادیر سرمی گلوکز، لیپید شامل کلسترول تام، تری‌گلیسرید، LDL، HDL، VLDL، نسبت LDL به HDL و کلسترول تام به LDL سنجیده شد.

**نتایج:** در تمام مقادیر گروه‌های تیماری با عصارۀ هیدروالکلی چویل، غلظت‌های گلوکز، تری‌گلیسرید کلسترول تام، LDL-c و نسبت LDL /HDL به‌طور معنی‌داری کاهش پیدا کرد. در حالی‌که غلظت HDL-c و نسبت کلسترول به LDL این گروه‌ها در مقایسه با گروه هیپرلیپیدمیک افزایش معنی‌داری داشت. اما کاهش معنی دار VLDL صرفاً در گروه تیماری mg/kg۵۰۰ عصاره هیدروالکلی چویر، مشاهده شد. اثرات هیپرلیپیدمیک و هیپوگلیسمیک عصارۀ چویر در مقادیر mg/kg ۵۰۰ و ۲۵۰ با اثرات آتورواستاتین و متفورمین قابل مقایسه بود.

**نتیجه‌گیری نهایی:** نتایج این مطالعه نشان‌دهندۀ اثرات هیپولیپیدمیک و هیپوگلیسمیک عصارۀ هیدروالکلی چویل به خاطر بالا بودن محتوای ترکیباتی از قبیل فنول، فلاونوئید و عناصر کم۲یاب باشد که قابلیت آنتی‌اکسیدانی داشته و بر مسیرهای آنزیمی سنتز و متابولیسم لیپیدها و گلوکز مؤثر واقع می‌شوند.

**واژه‌های کلیدی:** آتورواستاتین، عصارۀ گیاهی چویل، متفورمین، هیپرگلیسمی، هیپرلیپیدمی

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