

Hypolipidemic effect of dill seed (*Anethum graveolens L.*) essential oil on lipid profile and peroxisome proliferator-activated receptor- γ expression in hyperlipidemic male rats

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ABSTRACT

Herbal medicines have been suggested for the treatment of hyperlipidemic disorders. The hypolipidemic activities of dill essential oil on lipid profile and peroxisome proliferator-activated receptor- γ (PPAR γ) expression in adipose tissue were studied in male rats with hyperlipidemia. The effects were studied and compared of dill essential oil and atorvastatin on serum lipid profile and aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, histopathological damage of liver and PPAR γ gene expression in the adipose tissue of male rats with hyperlipidemia. The treatment with dill decreased body weight, serum cholesterol, triglyceride, LDL-C, ALT and AST levels, histopathological damage to the liver and PPAR γ expression of adipose tissue, and increased serum HDL-C levels in experimental hyperlipidemic rats compared to the hyperlipidemic control rats, both significantly. The plant and atorvastatin improved hyperlipidemia, attenuated liver tissue damage and down-regulated PPAR γ expression. So, dill could be defined as an excellent candidate for treatment of hyperlipidemia.

Key words: dill essential oil; atorvastatin; hyperlipidemia; PPAR γ ; rat

Introduction

Hyperlipidemia is recognized as elevated levels of serum lipids (LE, 2008). The liver daily produces 20-25% of total cholesterol and participates in cholesterol homeostasis. Hyperlipidemia is related to a deterioration in lifestyle and dietary habits, and it could be seen as an important risk factor for cardiovascular disease, atherosclerosis, stroke, and other diseases (GOTTO, 2011).

Large randomized controlled trials in hyperlipidemia treatment have provided evidence that reducing LDL-C concentrations with statins is efficient in both primary and secondary cardiovascular disease (CVD) prevention (REINER, 2013; TAYLOR et al., 2013). Statins are usually used by individuals with moderate or high CVD risk. However, statin therapy can cause significant

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cost to society. In addition, statin therapy is often related to the low treatment compliance and high rates of side effects (FARNIER and DAVIGNON, 1998; CALDERON et al., 2010).

Since ancient times, hyperlipidemia has been treated with medicinal plants. Recent scientific investigation has confirmed the efficacy of these preparations, some of which are remarkably effective, such as *Anethum graveolens*. *A. graveolens* or dill (local name: shevid) which belongs to the Apiaceae family (Umbelliferae), and is found in abundance in the East of Iran and South-eastern Europe. The phytochemical screening of this plant showed that its leaves are rich in tannins, steroids, terpenoids, saponins, flavonoids, and glycosides. The most important compounds from the fully grown seeds are β -carvone and limonene. These substances are attributed with the therapeutic effects of the plant, for ailments such as digestive disorders, bad breath, lactation problems, hypercholesterolemia, cancer, infection, diabetes, gastric problems, inflammation, antioxidant, and hypoglycemia (JANA and SHEKHAWAT, 2010; OSHAGHI et al., 2015; SATYANARAYANA et al., 2004). The anti-hyperlipidemic mechanisms of dill, however, are still unknown.

Peroxisome proliferator activated receptors (PPARs) are nuclear factors which participate in transcription. They bind to small molecules such as lipids, and control their gene expressions. Many factors, such as food compounds, activate PPARs which connect genes and environmental stimuli (RIGANO, et al., 2017). The separate genes encode three types of PPARs in mammals, and have high structural homology and level of sequence. The types of PPARs are defined as PPAR γ , $-\alpha$, and $-\beta$ (STAELS and FRUCHART, 2005). White adipose tissue highly expresses PPAR γ (BOCHER et al., 2002), where it is the important part of the transcriptional cascade underlying adipocyte differentiation. PPAR γ also plays an important role in the lipid metabolism in the adipose tissue. The activation of PPAR γ up-regulates genes which mediate fatty acid uptake and catching. PPAR γ may also promote cycling in adipocytes between triglyceride esterification and de-esterification (SEMPLE, et al., 2006).

It has been found that dill extract and its essential oil have hypolipidemic effects in rats (OSHAGHI et al., 2015). However, the mechanism of the effects has not yet been completely elucidated. It was indicated that dill seed extract suppresses diet-induced high-fat hyperlipidemia through hepatic PPAR α activation (TAKAHASHI et al., 2013). Considering the expanding use of herbs, the present study was conducted to investigate the effect of dill essential oil on abnormal lipid metabolism by expressing PPAR γ in the adipose tissue of hyperlipidemic male rats.

Materials and methods

Plant material. The essential oil of *Anethum graveolens* L. seeds was obtained from Barij Essence Company (Kashan, Iran), and its purity was found to be 99.8% based on gas chromatography mass analysis.

Chemicals. The reagents used for enzyme assays were commercial kits/products and reagents used for assays of serum parameters and were obtained from Parsazmoon Co (Tehran, Iran) and measured using a Cobas automated analyzer and the enzymatic method. All other chemicals and reagents were analytical grade and obtained from approved chemical suppliers. *Atorvastatin* (Merck, Germany) was resolved in saline at a dose of 10 mg/kg body weight. The essential oil was suspended in sunflower oil at doses of 0.5, 1 and 2 mL/kg body weight.

Animals. Adult male rats (180-200 g) were purchased from the Pasteur Institute (Karaj, Iran). They were kept in standard conditions (22 \pm 2 $^{\circ}$ C temperature, humidity of 40-60% and 12h light/12h dark cycle). All rats had access to food and water *ad libitum*. The ingredients of their diet are presented in Table 1 (prepared by Pars-Dam food service, Tehran, Iran). The present study was done in accordance with the guidelines for care and use of laboratory animals of the Varamin-Pishva Branch, Islamic Azad University, and the institutional guidelines for the care and use of laboratory animals (NIH, publication No. 85-23, revised 2010; European Communities Directive 86/609/EEC).

Table 1. The composition of the standard diet

Compound	Percent (%)
Casein	15.0
Sucrose	68.3
Hydrogenated coconut oil	10
Cellulose	2
Salts	4
Vitamins	0.5
Choline chloride	0.2

Hyperlipidemia induction and experimental groups. The rats were allowed to adapt to the conditions of the animal house for one week. Accordingly, six rats were kept in each separate cage (50 cm \times 23 cm). Hyperlipidemia was induced by adding 10% hydrogenated coconut oil to the diet (FERREIRA, et al., 2013) except for the normal control rats. The rats were divided into six groups (n=6 rats per group) randomly as follows: Group A: normal control group (intact); without treatment (n=6), group B: the hyperlipidemic control group; received 10% lipid diet and were given 0.5 mL sunflower oil as the vehicle of the essential oil by intragastric gavage, group C: control positive hyperlipidemic group; received 10% lipid diet and were given atorvastatin (0.01 g/kg, body weight by intragastric gavage), Groups D, E and F: experimental hyperlipidemic groups; received 10% lipid diet with the essential oil at doses of 0.5, 1 and 2 mL/kg, body weight by intragastric gavage.

Sampling. The animals were weighed every week. After 8 weeks of treatment, the rats were fasted for 12h and their final body weights were determined. Then, blood samples were drawn from the heart under light ether anesthesia. The liver samples were removed, weighed and fixed by 10% formalin-saline. The sampling of adipose tissue was done from abdominal fatty tissue for real time-PCR. The animals were sacrificed after sampling. The liver coefficient was obtained as the ratio of liver weight to body weight for each animal. Serum lipids, including cholesterol, triglyceride (TG), LDL-C, HDL-C, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, were determined using a kit (Parsazmoon Company, Iran).

Histo-pathological study. For qualitative analysis of liver histology, the tissue samples were fixed for 48h in 10% formalin-saline and dehydrated by passing them successfully through different mixtures of ethyl alcohol-water, cleaned in xylene, and embedded in paraffin. Sections of the tissue were prepared using a rotary microtome (5 μ thickness), and stained with haematoxylin and eosin dye. All data are presented as the mean value \pm SD of the six rats.

All histo-pathological damage, including fatty changes to hepatocyte, sinusoid dilation, and congestion, were given score 1 and then the total scores were obtained for each section.

Gene expression analysis. After the rats were sacrificed, the abdominal adipose tissue was rapidly excised and frozen in liquid nitrogen and stored at -80 C for study of mRNA. Total mRNA was prepared separately from the adipose tissue of individual rats, using Trizol (Invitrogen, Australia). The relative level of specific mRNA was assessed by reverse transcriptase polymerase chain reaction (RT-PCR) (OH et al., 2019). Single-stranded cDNA was synthesized from 1 μ g of total RNA using Super Script II RNase H reverse transcriptase as per the manufacturer's instructions (Invitrogen, Australia). PCR was performed on a thermo-cycler PTC-200 DNA engine (MJ Research Inc., MA, USA). The required cDNA was synthesized with Platinum Pfx DNA Polymerase (Invitrogen, Australia). The gene examined was PPAR γ (NM06238; 177 bp; sense: 5'-ACAGCATGCACTTCCTTCCA-3' and antisense: 5'-TCACATGCATGAACACCGTA-3') and the house-keeping gene was GAPDH (NM-017008.3; 193 bp; sense: 5'-CCATCAA CGACCCCTTCATT-3' and antisense: 5'-CACG ACATACTCAGCACCAGC-3') from the adipose tissue. The results shown are representative of a pool RNA population of 6 rats per group. The PCR samples were electrophoresed on 3% agarose gel and stained with ethidium bromide. The gel images were captured digitally with a CCD camera and analyzed using Image J 1.29 (NIH, USA).

Statistical analysis. All data were analyzed by one-way ANOVA and GraphPad Prism v7.03 (GraphPad Software Inc., USA) and presented as the mean value \pm S.D. of six rats (n=6). A P value

less than 0.05 was considered significant. The level of gene expression of PPAR γ (fold change) was measured by this formula:

$$\text{Fold change} = 2^{-\Delta\Delta\text{ct}}$$

Results

Body weight and liver coefficients. Changes in initial and final body weights (weight gain) in the control and experimental groups are shown in Table 2. The results show the treatments of dill and atorvastatin decreased weight gain in comparison to the hyperlipidemic control group ($P < 0.001$ and $P < 0.01$, respectively). The results show treatment with dill and atorvastatin did not affect liver coefficients significantly in comparison to the hyperlipidemic control group.

Serum biochemical parameters. The administration of the essential oil (0.5, 1 and 2 mL/kg, body weight) and atorvastatin significantly decreased serum triglycerides and cholesterol (Table 3), LDL-C (Table 4), ALT and AST levels (Table 5), while increasing serum HDL-C levels (Table 4) in hyperlipidemic rats compared with the hyperlipidemic control group.

Histo-pathological study. Histopathological results showed that treatment with the essential oil (0.5, 1 and 2 mL/kg, body weight) and atorvastatin (0.01 g/kg) significantly decreased histopathological damage to the liver in the experimental hyperlipidemic groups compared with the hyperlipidemic control group (Fig. 1, Fig. 2).

Table 2. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 0.01 g/kg on weight gain and liver coefficients in hyperlipidemic male rats

Groups	Weight gain (g)	Liver coefficient
Normal control	58.6 ± 12	0.028 ± 0.004
Hyperlipidemic control	91.6 ± 11 **	0.027 ± 0.002
Atorvastatin	56.8 ± 21.2 ++	0.026 ± 0.001
Dill oil (mL/kg)		
0.5	49 ± 13 +++	0.029 ± 0.002
1	52 ± 12 +++	0.032 ± 0.002
2	59 ± 18 ++	0.029 ± 0.003

All data are presented as the mean value ± S.D. of six rats. ** $P < 0.01$ different from the normal control group, ++ $P < 0.01$, +++ $P < 0.001$ different from the hyperlipidemic control group

Table 3. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 0.01 g/kg on serum triglycerides and cholesterol levels in hyperlipidemic male rats

Groups	Triglycerides (mg/dL)	Cholesterol (mg/dL)
Normal control	56.1 ± 8.8	49.8 ± 6.4
Hyperlipidemic control	81.6 ± 10 *	73.2 ± 8.4 ***
Atorvastatin	52.2 ± 11.4 +	53.6 ± 9.5 +++
Dill oil (mL/kg)		
0.5	53 ± 19 +	59 ± 7 +
1	49 ± 22 ++	53 ± 5 +++
2	54 ± 15 +	52 ± 10 +++

All data are presented as the mean value ± S.D. of six rats. * $P < 0.05$, *** $P < 0.001$ different from the normal control group, + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.01$ different from the hyperlipidemic control group

Table 4. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 0.01 g/kg on serum LDL-C and HDL-C levels in hyperlipidemic male rats

Groups	LDL-C (mg/dL)	HDL-C (mg/dL)
Normal control	4 \pm 2.9	40.2 \pm 4.4
Hyperlipidemic control	9.5 \pm 3.4 ***	30.2 \pm 2.1 *
Atorvastatin	3.2 \pm 2.1 +++	38.5 \pm 4.4
Dill oil (mL/kg)		
0.5	5.5 \pm 0.5 +++	41 \pm 5 ++
1	4.2 \pm 1 +++	44 \pm 5 +++
2	3 \pm 1 +++	49 \pm 9 +++, #

All data are presented as the mean value \pm S.D. of six rats. *P<0.05, *** P<0.001 different from the normal control group, ++P<0.01, +++ P<0.01 different from the hyperlipidemic control group, # P<0.05 different from atorvastatin group

Table 5. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 0.01 g/kg on serum ALT and AST levels in hyperlipidemic male rats

Groups	ALT (UI/L)	AST(UI/L)
Normal control	46 \pm 11	138.6 \pm 15.9
Hyperlipidemic control	71.7 \pm 15.6 **	198.2 \pm 10 *
Atorvastatin	63.2 \pm 9.6	132.3 \pm 13.6 ++
Dill oil (mL/kg)		
0.5	51 \pm 17 +	174 \pm 60
1	46 \pm 7 ++	130 \pm 51 ++
2	44 \pm 11 ++	117 \pm 12 +++

All data are presented as the mean value \pm S.D. of six rats. *P<0.05, **P<0.01 different from the normal control group, +P<0.05, ++P<0.05, +++ P<0.01 different from the hyperlipidemic control group

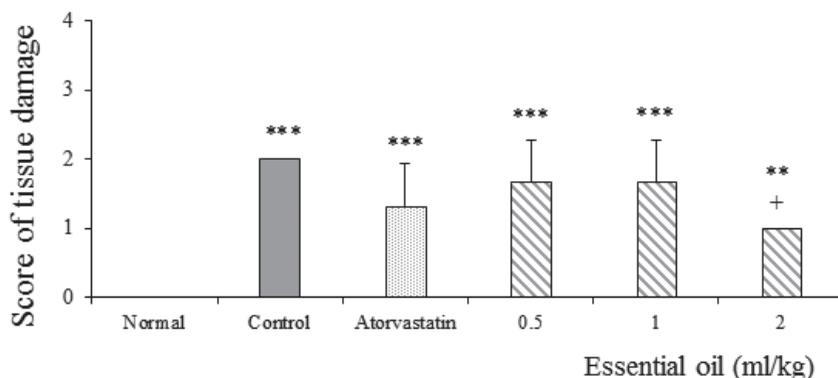


Fig. 1. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 0.01 g/kg on liver tissue damage scores in hyperlipidemic male rats

*** P<0.001 different from the normal group, + P<0.05 different from the hyperlipidemic control group. Each column represented mean value \pm SD of six rats

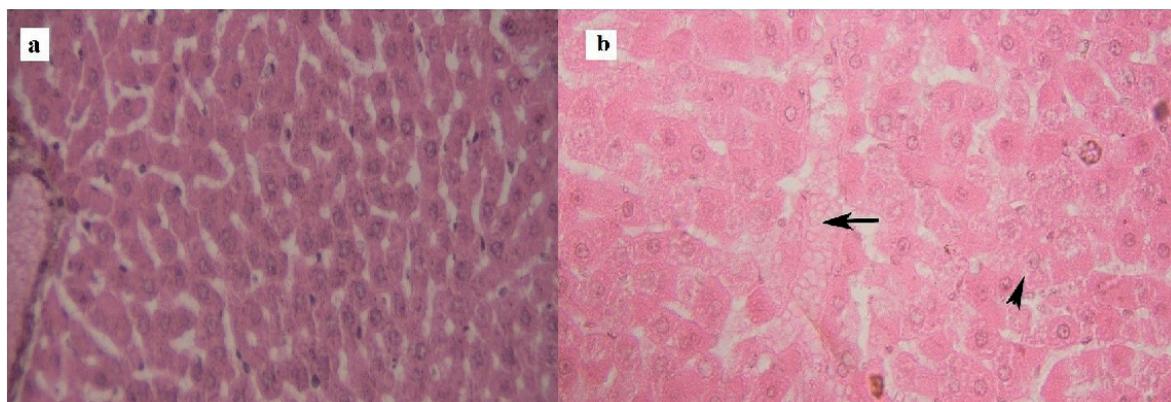


Fig. 2. Histopathology of liver tissue in normal and hyperlipidemic rats (hematoxylin-eosin) a: Normal liver tissue of normal control group ($\times 100$), b: fatty change in hepatocyte (Tip arrows), Hyperemia of hyperlipidemic control group (Arrows) ($\times 100$)

Real time PCR. The administration of the essential oil (0.5, 1 and 2 mL/kg, body weight) significantly decreased PPAR γ expression in the experimental hyperlipidemic groups compared

with the hyperlipidemic control group ($P < 0.001$). The effect of dill essential oil was more potent than atorvastatin ($P < 0.001$) (Fig. 3).

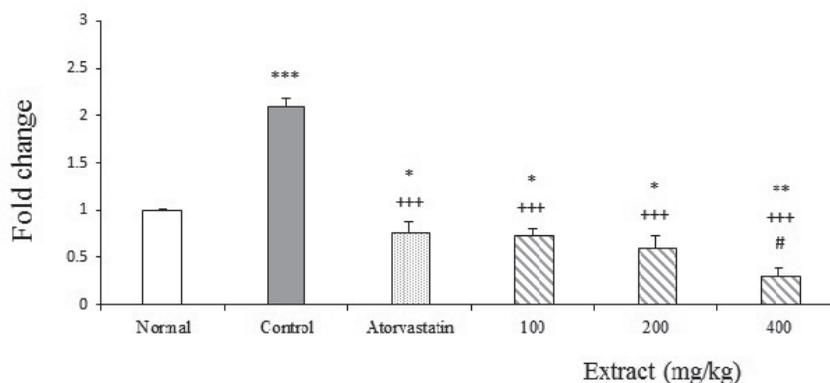


Fig. 3. Effects of dill at doses of 0.5, 1 and 2 mL/kg and atorvastatin at a dose of 10 g/kg on PPAR γ expression ratio in adipose tissue of hyperlipidemic male rats

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ different from the normal group, +++ $P < 0.001$ different from the hyperlipidemic control group, # $P < 0.001$ different from the atorvastatin group. All data are presented as the mean value \pm S.D. of six rats

Discussion

The present study showed that the essential oil from dill seeds improved serum lipid profile, attenuated histo-pathological damage to the liver, and down-regulated PPAR γ gene expression in the adipose tissue of treated hyperlipidemic rats.

In agreement, MIRHOSSEINI et al. (2014) applied dill tablets and gemfibrozil for 2 months to 91 hyperlipidemic patients. The results showed total cholesterol and triglyceride were significantly reduced. Also, HDL levels in the serum were not affected, and gemfibrozil reduced triglyceride and increased HDL more than dill. Dill attenuated serum total cholesterol levels more than gemfibrozil. The results showed that dill has hypocholesterolemic and hypotriglycemic effects in patients.

HAMEDI et al. (2017) evaluated the hypolipidemic effect of hydrosol beverages of medicinal plants in Fars province. The results indicated that the effects of barberry, fumitory, dill, and aloe hydrosols have more potent effects than other plants. MOLLAZADEH et al. (2019) reported that *Anethum graveolans* has the best triglyceride lowering effect of medicinal plants. LEE et al. (2019) showed that oral treatment with enzyme-treated *Chrysanthemum indicum* Linné at various doses for 7 weeks decreased body weight, serum lipid profile including TG, total cholesterol, LDL and leptin in a dose-dependent manner, but not serum HDL levels or adiponectin in the hyperlipidemic mice. *Chrysanthemum indicum* significantly decreased lipid levels in the liver and the size of adipocytes in the white adipose tissue around the epididymis. Also, the plant effectively down-regulated transcription factors such as PPAR γ and CCAAT/enhancer binding protein- α (C/EBP- α) and up-regulated PPAR- α in the liver and epididymal white adipose tissue. KARSONO et al. (2019) indicated the antiadipogenic effect of bioactive fractions from *Lagerstroemia speciosa* leaves, mediated by significant down-regulation of mRNA level of PPAR γ . This fraction has inhibitory activity in adipogenesis and lipogenesis, and may provide potentially effective benefits in the prevention of obesity. TAKAHASHI et al. (2013) reported that dill seed extract suppresses hyperlipidemic conditions by hepatic PPAR α

activation in high-fat diet-induced hyperlipidemic rats. HONORÉ et al. (2018) investigated the anti-obesity effects of *Smallanthus sonchifolius* roots in hyperlipidemic rats. The plant attenuated weight gain, decreased visceral fat pad weight, and restored the serum lipid profile and atherogenic index. Also, it was shown that treated rats had lower glucose and insulin levels, improved glucose tolerance, and insulin sensitivity. Down-regulation occurred of some factors of adipocyte specific-transcription, including PPAR γ 2, C/EBP- α , activating protein (aP2) mRNA levels in the visceral adipose tissue. So, the results showed the anti-obesity properties of yacon through inhibition of adipogenesis and improvement of visceral adipose tissue function. HONG et al. (2018) showed that *Glehnia littoralis* root extract inhibited the differentiation of 3T3-L1 adipocyte and intracellular lipid accumulation in differentiated adipocytes of obese mice. The extract decreased body weight gain and fat accumulation, and the expression of adipogenic genes, such as PPAR γ , C/EBP α , fatty acid synthase and fatty acid synthase. These findings showed that the plant down-regulated the adipogenic gene expression in adipocytes. OH et al. (2019) showed *Artemisia princeps* extract affected adipocyte differentiation, and then reduced lipid accumulation and down-regulation of PPAR γ . *Artemisia princeps* extract effectively reduced mRNA and protein expression of PPAR γ , C/EBP α , and SREBP-1c. *A. princeps* extract reduced levels of phosphorylated p38, ERK, and JNK. Overall, the extract was observed to suppress adipogenesis-related signaling in 3T3-L1 cells. The promising ability of *Artemisia princeps* extract to inhibit adipocyte differentiation of 3T3-L1 cells suggests that *Artemisia princeps* has potential as a source of anti-obesity compounds.

The PPAR γ pathway is the main regulator of adipocyte differentiation and consists of several transcription factors and proteins, such as C/EBP α and SREBP-1c (PAYNE et al., 2009). Suppression of PPAR γ activation and inhibition of its transcription factor expression was shown to hinder adipogenesis, resulting in a lower adipocyte profile and decreased fat storage in differentiating adipocytes (CHRISTODOULIDES and VIDAL-

PUIG, 2010). GUO et al. (2019) showed that hexane extracts of *Petasites japonicus* reduced glucose uptake, and inhibited adipogenesis and triglyceride accumulation in 3T3-L1 cells through down-regulation of the expression of PPAR γ and its target genes. VARIYA et al. (2019) showed that treatment with *Emblica officinalis* fruit juice and gallic acid facilitated glucose homeostasis, improved insulin sensitivity, reduced obesity, abridged elevated blood pressure, and decreased cholesterol levels, and also induced adipogenesis in 3T3-L1 adipocytes. Mechanistically, treatment increased the expression of PPAR γ through activation of C/EBPs, and simultaneously increased Glut4 translocation in 3T3-L1 adipocytes. Moreover, gallic acid treatment increased insulin sensitivity through activation of Akt rather than the AMPK signaling pathway while fruit juice of *E. officinalis* showed dual activation of both Akt and AMPK. These findings reveal the role of gallic acid in potential *E. officinalis* mediated antidiabetic therapy, and delineate the up-regulation of pAkt, PPAR- γ and Glut4 in gallic acid mediated antidiabetic activity, thus providing potential therapy for diabetes and related disorders. BALAKRISHNAN et al. (2018) showed *Moringa concanensis* Nimmo has antidiabetic, antihyperglycemic, hypoglycemic properties, and is a potential insulin sensitizer (PPAR γ , C/EBP- α /Akt over expression). MITANI et al. (2017) showed a caffeine-conditioning medium decreased lipid accumulation and suppressed gene expression of proliferator activated receptor (PPAR) γ and CCAAT/enhancer binding protein (C/EBP) α in 3T3-L1 adipocytes. GERMOUSH et al. (2020) showed *Padina pavonia*-derived terpenes attenuated hyperglycemia, dyslipidemia, oxidative stress, and inflammation, and improved insulin sensitivity and carbohydrate metabolism in type 2 diabetic rats via PPAR γ activation.

Conclusions

The present study reveals that the essential oil of *Anethum graveolens* can serve as a potential candidate for the management of hyperlipidemia. It exerted inhibitory effects on adipocyte differentiation. As shown in molecular analysis, the plant treatment decreased the mRNA levels

of PPAR γ , which is involved in adipocytes differentiation. The plant was also able to down-regulate the gene expression. Further studies are being carried out to validate its effects on other biological process related to adipocyte biology.

Conflict of Interest

All the authors declare that they have no conflict of interest.

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Ethical approval

All experimental procedures were conducted in accordance with the guidelines for the care and use of laboratory animals observed at the Science and Research Branch, Islamic Azad University and were in agreement with the institutional guidelines for the care and use of laboratory animals (NIH, publication No. 85-23, revised 2010; European Communities Directive 86/609/EEC).

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SAŽETAK

Za hiperlipidemijske poremećaje preporučuju se biljni lijekovi. U masnom tkivu mužjaka štakora s hiperlipidemijom istraženo je hipolipidemijsko djelovanje esencijalnog ulja kopra na lipidni profil i ekspresiju receptora γ koji aktivira proliferator peroksisoma (PPAR γ). Uspoređeni su učinci esencijalnog ulja kopra i atorvastatina na lipidni profil seruma te vrijednosti aspartat-aminotransferaze (AST), alanin-aminotransferaze (ALT), histopatološko oštećenje jetre i ekspresiju gena PPAR γ u masnom tkivu mužjaka štakora s hiperlipidemijom. Primjena esencijalnog ulja kopra smanjila je tjelesnu masu, serumski kolesterol, vrijednosti triglicerida, razine LDL-C, ALT-a i AST-a, te je također utjecala na smanjenje histopatološkog oštećenja jetre i ekspresiju PPAR γ u masnom tkivu, dok je istodobno znakovito povećan serumski HDL-C u pokusnoj skupini štakora u usporedbi s kontrolnom skupinom hiperlipidemičnih štakora. Biljni pripravak i atorvastatin pozitivno su utjecali na hiperlipidemiju, atenuirano oštećenje jetrenog tkiva i smanjenje ekspresije PPAR γ . Zaključuje se da bi kopar mogao biti izvrstan kandidat za sredstvo u liječenju hiperlipidemije.

Ključne riječi: esencijalno ulje kopra; atorvastatin; hiperlipidemija; PPAR γ ; štakor
