

## Effects of *Anethum graveolens* leave powder on lipid profile in hyperlipidemic patients

### *Anethum graveolens* yaprak tozununun hiperlipidemik hastalardaki lipit profili üzerine etkileri

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#### SUMMARY

**AIM:** The appearance of adverse effects result in discontinuation of statins by patients which lead to recurrent hyperlipidemia. This may encourage efforts to look for new and safe hypolipidemic agent, many plants used in folk medicine thought to have hypolipidemic effect. *Anethum graveolens* (Dill) is an annual herb cultivated in Iraq used both as medicinal agent and as food spice. The present study was designed to determine the effect of *Anethum graveolens* leave powder on lipid profile in the serum of hyperlipidemic patients, compared with that of standard antihyperlipidemic agent lovastatin.

**METHODS:** A prospective randomized clinical trial was carried out on 30 hyperlipidemic patients who attend to outpatient clinic in Al-Kindy College of Medicine, Baghdad, Iraq, over the period from January 2012 to June 2012. Patients were allocated into: Group A composed of 15 patients treated with lovastatin tablets 20mg once daily for four weeks period; Group B composed of 15 patients treated with 500 mg *Anethum graveolens* crude powder capsules, to be taken twice daily for four weeks period; besides 15 healthy subjects serve as control. Blood samples were collected after overnight fasting to check the changes in lipid profile.

**RESULTS:** Administration of *Anethum graveolens* leave powder results in highly significant reduction of lipid profile in hyperlipidemic patients, besides reduction of atherosclerotic index. Its effect is comparable to that of standard agent lovastatin.

**CONCLUSION:** Results obtained in this study suggesting that *Anethum graveolens* is an efficient hypolipidemic agent and promising cardioprotectant agent. This study clearly showed the strong scientific clinical basis for hypolipidemic traditional use of *Anethum graveolens*.

**Key words:** Hyperlipidemia, *Anethum graveolens*, statins, herbal medicine.

#### ÖZET

**AMAÇ:** Yan etkilerin görülmesi, hastalar tarafından statinlerin kesilmesiyle tekrarlayan hiperlipidemiyle sonuçlanır. Bu, yeni ve güvenli hipolipidemik ajanlar, hipolipidemik etkiye sahip olduğu düşünülen halk tıbbında kullanılan birçok bitkiyi gözden geçirmeye teşvik edebilir. *Anethum graveolens*, tedavi ajanı ve baharat olarak kullanılan, Irak'ta yetişen yıllık bir bitkidir. Şimdiki çalışma, hiperlipidemik hastaların serumlarındaki lipit profili üzerine olan etkilerinin standart antihiperlipidemik ajan lovastatininki ile karşılaştırıldığı *Anethum graveolens* yaprak tozlarının etkilerini saptamak için dizayn edildi.

**YÖNTEM:** Ocak 2012-Haziran 2012 dönemi boyunca Irak Bağdat Al-Kindy Tıp Koleji'nde kliniğe dışarıdan gelen 30 hiperlipidemik hasta üzerinde prospektif randomize bir klinik çalışma gerçekleştirildi. Hastalar, 4 hafta boyunca günde bir defa 20 mg lovastatin tabletleri ile tedavi olan 15 hastadan oluşan Grup A; 4 hafta boyunca günde iki defa alınan 500 mg'lık *Anethum graveolens* ham tozu kapsülü ile tedavi edilen 15 hastadan oluşan Grup B ve 15 sağlıklı denekten oluşan kontrol gruplarına ayrıldı. Lipit profilindeki değişiklikleri kontrol etmek için kan numuneleri bir gecelik açlık sonrası toplandı.

**BULGULAR:** *Anethum graveolens* yaprak tozu uygulaması, aterosklerotik indeksteki azalma yanında hiperlipidemik hastalarda lipit profilinde belirgin bir azalma ile sonuçlandı. Etkisi, standart ajan lovastatin ile karşılaştırılabilecek düzeydedir.

**SONUÇ:** Bu çalışmada elde edilen sonuçlar, *Anethum graveolens*'in etkili bir hipolipidemik ajan ve umut verici kalp koruyucu ajan olduğunu önermektedir. Bu çalışma *Anethum graveolens*'in hipolipidemik geleneksel kullanımı için güçlü bilimsel klinik temelini açıkça göstermiştir.

**Anahtar kelimeler:** Hiperlipidemi, *Anethum graveolens*, statinler, bitkisel tedavi.

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## INTRODUCTION

Hyperlipidemia is highly prevalent disorder and is a major cause of atherosclerosis; it is closely related to coronary heart disease which is the most common cause of death worldwide [1]. Thus, dyslipidemia is a risk factor which led to the development of hypolipidemic drugs [2]. One of the highly efficacious hypolipidemic drugs, are statins. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the rate limiting step in cholesterol biosynthesis [3]. Statins group considered one of the safest hypolipidemic drugs; but no drug provides health benefits without some degree of risk, and risk-benefit assessments require ongoing review as new data become available. This is certainly the case for the use of statins. So many patients end statins use due to their adverse effects [4].

The most severe adverse effect of statins is myotoxicity, as myopathy, myalgia, myositis or rhabdomyolysis. Clinical trials commonly define statin toxicity as myalgia or muscle weakness with creatine kinase (CK) levels greater than ten times the normal upper limit. Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure, disseminated intravascular coagulation and death. The exact pathophysiology of statin-induced myopathy is not fully known. Multiple pathophysiological mechanisms may contribute to statin myotoxicity [5, 6].

Recently, there is a total of large clinical trials support the notion that statins modestly increase the risk of incident diabetes. Because diabetes is a risk equivalent condition for coronary and peripheral arterial diseases, these findings create a paradox whereby needed statin therapy may be withheld to avoid excess risk of diabetes while representing the strongest cardiovascular risk reduction tool in diabetics [7].

The appearance of adverse effects result in discontinuation of statins by patients which lead to recurrent hyperlipidemia, this may encourage the patients to look for new and safe hypolipidemic agent, and it is not a surprise to be shifted to the herbal folk medicine [8, 9].

Research in herbal medicine has increased in the world as alternative solution to health problems; furthermore, side effects of drugs in current use, besides unsatisfaction of patients with results obtained when using classical drugs shift the orientation toward herbal medicine, especially high percent of people thought that using of herbal medicine is free of side effect [10].

Many plant extract have been shown to have hypolipidemic effect in experimental animals [11]. *Anethum graveolens* (AG) Umbelliferae, known as Dill, is an annual herb growing in the Mediterranean region, Europe, central and southern Asia; the plant is used both as medicinal agent and as food spice. Dill has been used traditionally for gastrointestinal disturbances such as flatulence, indigestion and colic [12]. In Iraq, Dill was used as food spice and in Grape Water for children as antifatulent.

The active constituents of AG have been classified as flavonoids, phenolic compounds, and essential oils, the phytochemical screening of plant showed that leaves, stems and roots were rich in tannins, terpenoids, cardiac glycosides and flavonoids [13-15]. Pharmacological effects of AG include antibacterial [16], antifungal [17], antispasmodic [18], antisecretory and mucosal protective effects [19]. The antihyperlipidemic activity of crude extract has previously been reported [20].

The present study was designed to determine the effect of AG leave powder on lipid profile in the serum of hyperlipidemic patients, compared with that of standard antihyperlipidemic agent lovastatin.

## MATERIAL AND METHODS

A prospective randomized clinical trial was carried out on 30 hyperlipidemic patients of both sexes with age range 44-63 years, with disease duration of 5-10 years, who attend to outpatient clinic in Alkindy College of Medicine for a period of six months from January 2012-June 2012; the study was approved by scientific and ethical committee in Alkindy College of Medicine/University of Baghdad, an informed consent was taken from all the patients. All patients were kept on diet control program under the supervision of dietary specialist. Patients with chronic disease, diabetes mellitus, and ischemic heart diseases, liver diseases, renal disease, and pregnant woman were excluded from this study, hyperlipidemic patients taking other type of hyperlipidemic agents also excluded from this study. Patients participate in this study were allocated into two groups:

Group A: composed of 15 patients treated with lovastatin tablets 20 mg once daily for 4 weeks period.

Group B: composed of 15 patients treated with AG crude powder prepared as capsules, each capsule contains 500 mg of fine powder of AG leaves obtained from local markets, to be taken twice daily

for four weeks period. Besides that, 15 healthy subjects of matched age and sex to patients were enrolled in the study and serve as control.

Blood samples were collected from all patients by venepuncture after overnight fasting and this value designed to be the pre-treatment value, in addition to that blood samples were taken at the end of 4<sup>th</sup> week also after overnight fasting to check the changes in the total serum cholesterol (TC), serum triglyceride (TG), serum high density lipoprotein cholesterol (HDL-C) levels; serum low density lipoprotein cholesterol (LDL-C) levels and serum very low density lipoprotein cholesterol (VLDL-C) levels; which were measured according to the standard methods.

Statistical analysis of data was done using student t-test and *P* value lower than 0.05 were considered significant, and *P* value lower than 0.01 were considered highly significant.

and 44.7% respectively (Table1, Figure1); besides that, there is only significant *P*≤0.05 reduction in TG level by 12.7%; while there is significant *P*≤0.05 elevation in serum level of HDL-C by 17.8% after four weeks treatment period.

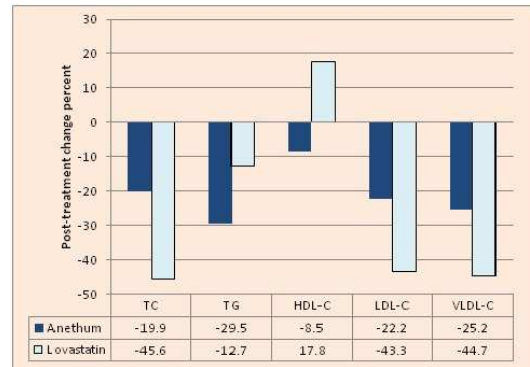


Figure 1. Post treatment changes in lipid profile.

**RESULTS**

The pre-treatment values of serum lipids for both treatment groups were significantly *P*≤0.05 higher than that of control; except that of HDL-C which was non-significantly lower than control (Table 1). Treatment of hyperlipidemic patients with AG leave powder for four weeks duration results in highly significant *P*≤0.01 reduction in the values of TC, TG, LDL-C and VLDL-C; the percent reduction were 19.9%, 29.5%, 22.2% and 25.2% respectively (Table1, Figure1). Concerning HDL-C, treatment with AG non-significantly reduces its serum level by only 8.5%.

On the other hand, treatment of hyperlipidemic patients with the standard hypolipidemic agent lovastatin results in highly significant reduction *P*≤0.01 in the serum levels of TC, LDL-C and VLDL-C, the percent reduction were 45.6%, 43.3%

Table 2 and Figure 2 showed the changes in lipid ratios of the studied groups compared with healthy control. Results obtained showed that the calculated ratios of lipid namely TG/HDL-C, TC/HDL-C and LDL-C/HDL-C were significantly higher in all hyperlipidemic patients compared to healthy subjects; Treatment of hyperlipidemic patients with AG significantly *P*≤0.05 decreased TC/HDL-C and LDL-C/HDL-C after four weeks of treatment, at the same time highly significant *P*≤0.01 reduction in TG/HDL-C even to less than that of healthy control. In contrast, treatment with lovastatin significantly *P*≤0.05 decreased all lipid ratios in hyperlipidemic patients after four weeks duration. During the course of treatment, any type of side effects were not recorded indicating the safety and tolerability of administered agent.

Table 1: Effects of *Anethum graveolens* and lovastatin on lipid profile.

Variables (mmol/L)	Control, n=15	Group B			
		<i>Anethum graveolens</i> , n=15		Group A	
		Pre	Post	Pre	Post
TC	3.67±0.12	6.08±0.41 <sup>¶</sup>	4.87±0.48 <sup>**</sup>	7.76±0.38 <sup>¶</sup>	4.22±0.28 <sup>**</sup>
TG	1.82±0.08	2.03±0.57 <sup>¶</sup>	1.43±0.4 <sup>**</sup>	2.91±0.35 <sup>¶</sup>	2.54±0.4 <sup>*</sup>
HDL-C	1.46±0.07	1.41±0.32	1.29±0.08	1.12±0.04	1.32±0.05 <sup>*</sup>
LDL-C	2.76±0.2	3.78±0.48 <sup>¶</sup>	2.94±0.47 <sup>**</sup>	4.18±0.26 <sup>¶</sup>	2.37±0.31 <sup>**</sup>
VLDL-C	0.51±0.12	0.87±0.2 <sup>¶</sup>	0.65±0.18 <sup>**</sup>	0.96±0.13 <sup>¶</sup>	0.53±0.2 <sup>**</sup>

Results represent Mean±SD.

¶ Significantly (*P*≤0.05) different with respect to control.

\* Significantly (*P*≤0.05) different with respect to pre-treatment value.

\*\* Highly Significantly (*P*≤0.01) different with respect to pre-treatment value.

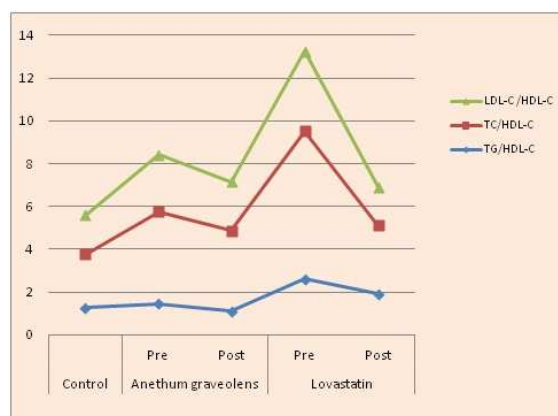
**Table 2:** Effects of *Anethum graveolens* and Lovastatin on lipid ratios.

Variables	Control, n=15	Group B <i>Anethum graveolens</i> , n=15		Group A Lovastatin, n=15	
		Pre	Post	Pre	Post
TG/ HDL-C	1.25	1.44 <sup>‡</sup>	1.1**	2.6 <sup>‡</sup>	1.92*
TC/ HDL-C	2.51	4.31 <sup>‡</sup>	3.77*	6.93 <sup>‡</sup>	3.19*
LDL-C/ HDL-C	1.84	2.68 <sup>‡</sup>	2.28*	3.73 <sup>‡</sup>	1.79*

<sup>‡</sup>Significantly ( $P \leq 0.05$ ) different with respect to control.

\*Significantly ( $P \leq 0.05$ ) different with respect to pre-treatment value.

\*\*Highly Significantly ( $P \leq 0.01$ ) different with respect to pre-treatment value.



**Figure 2.** Comparison of lipid ratios between control, *Anethum graveolens* and lovastatin.

## DISCUSSION

Hyperlipidemia, the major cause of atherosclerosis, which is an important risk factor of ischemic heart disease, can be treated with different groups of drugs. During the last decade there is a special interest in herbal medicine in an effort to develop new drugs for the treatment of big health disorder like hyperlipidemia, especially high percent of public belief that herbal medicine is safe and free of side effects. Many plants have been shown to have antihyperlipidemic activity, AG is one of the most used plants as food and spice are thought to have antihyperlipidemic activity, scientific studies about this effect are very rare that not exceed the number of one hand fingers, search in Pubmed and Google Scholar for antihyperlipidemic activity of AG revealed only five reports among which only one study was carried out on human as a randomized

clinical trial and the other four studies were done on rats, surprisingly, all the five studies were done in Iran, since AG is used widely as antihyperlipidemic agent in Iranian folk medicine, these studies showed a big contradiction in their results [21].

The results of the first study which is carried out on rats reported that administration of water extract of AG leaves for 14 consecutive days reduced the TG and TC levels by 50 and 20% respectively [20]. The remaining animal studies [22-24] demonstrated that administration of AG to hyperlipidemic rats significantly reduced TC, TG and LDL-C levels and significantly increased the level of good cholesterol HDL-C. On the contrary, administration of AG to hyperlipidemic patients showed opposite results to that of animals as reported by Kojuri *et al.* [25]; where it has been shown that after administration of anethum tablets (650 mg) twice daily for six weeks results in non-significant reduction of TC and LDL-C levels, while there was increase in TG level, at the same time HDL-C level shown to be decreased.

In the present study, administration of AG leave powder as capsules containing 500 mg twice daily results in highly significant reduction of TC, TG, LDL-C and VLDL-C serum levels besides non-significant reduction of HDL-C level which is controversial results when compared with the above mentioned studies. On the other hand, treatment of hyperlipidemic patients with lovastatin results in significant reduction in TG level and significant increase in HDL-C level compared to AG group. Furthermore, results of this study showed that the atherosclerotic index LDL-C/HDL-C significantly decreased in both groups indicating the clinical advantages of both agents to decrease the incidence of ischemic heart diseases since LDL-C/HDL-C ratio is strongly correlated with cardiovascular diseases. On the other hand, TC/HDL-C ratio also significantly decreased in both groups; recently it has been shown that small, dense LDL-C particles penetrate the vascular endothelium more easily and accelerate the atherosclerotic process [26]; in addition to that, recent report demonstrated that calculation of TG/HDL-C ratio could be used as a simple, indirect and feasible indicator of LDL-C particles size and it is significantly associated with atherogenic dyslipidemia [27]. In this study, administration of AG results in highly significant reduction both in serum level of TG and in TG/HDL-C ratio compared to lovastatin which only significantly reduce them, indicating the clinical advantages of AG over lovastatin, this finding contributes partially as a scientific basis for use of AG as antihyperlipidemic agent.

Concerning the mechanisms by which AG exert its hypolipidemic effects; there was no definite mechanism documented so far, Haghghi *et al.* investigate the hepatic phosphatidate phosphohydrolase enzyme activity as proposed pathway for the hypolipidemic effect of AG constituent, but the results obtained were negative, they proposed that the major components of AG are flavonoides such as carvon, limonene, or  $\alpha$ -phellandrene which are responsible for the biological effect of AG possibly through affecting the key enzymes such as HMG-CoA reductase or acyl CoA carboxylase [28]. It has been suggested that anethum components may also increase LDL receptors in the liver stimulating cholesterol clearance from the blood; many other suggestions including a decrease in cholesterol absorption from the intestine; in addition, the observed hypotriglyceridemic effect might be due to a decrease in fatty acid synthesis [29]. Furthermore, AG may improve hypercholesterolemia by modification of lipoprotein metabolism mainly through enhancement of lipoprotein metabolism [23]. On the other hand, it has been proposed that AG exerts its hypolipidemic effect via antioxidant effect [30, 31]; where it has been reported that AG might have hepatoprotective effect against harmful effects of oxidized fats due to polyphenol contents of AG [32]. Determination of the exact mechanism by which AG exerts its hypolipidemic effect needs further deep investigation on molecular level, while large scale clinical trials with large sample size and multicenter studies are needed to clarify the role of AG as hypolipidemic agent.

## CONCLUSION

In conclusion, administration of AG leave powder 500 mg twice daily results in highly significant reduction in lipid profile and atherosclerotic index suggesting a promising cardioprotective agent, this study clearly showed the strong clinical basis for hypolipidemic traditional use of *Anethum graveolens*.

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