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Anethum graveolens Supplementation Improves Insulin Sensitivity and Lipid Abnormality in Type 2 Diabetic Patients

Majid Mobasseri[1], Laleh Payahoo[2*], Alireza Ostadrahimi[3], Yaser Khaje bishak[2], Mohammad Asghari Jafarabadi[4], Sepide Mahluji[2]

[1]*Bone Research Center, Tabriz University of Medical Science, Tabriz, Iran.*

[2]*Student Research Committee, Moje Danesh, Tabriz University of Medical Science, Tabriz, Iran.*

[3]*Nutrition Research Center, Tabriz University of Medical Science, Tabriz, Iran.*

[4]*Health Management Research Center, Tabriz University of Medical Science, Tabriz, Iran.*

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ABSTRACT

Background: Using of herbs as complementary medications for treatment of diseases has been prevailed in the world. This study was aimed to investigate the effects of Anethum supplementation on insulin sensitivity, fasting blood glucose (FBS) and lipid profile in type 2 diabetic patients. ***Methods:*** This randomized-double blind- placebo-controlled study was conducted on 60 diabetic patients in Tabriz, Iran from January to March 2012. Intervention group received 3.3 g/day powder of Anethum for 8 weeks. Fasting blood glucose, Triglyceride (TG), Total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) levels were assessed by enzymatic colorimetric method at onset and at the end of study. Serum insulin level was determined by ELISA method and HOMA-IR as an index of insulin resistance calculated as fasting concentrations of blood glucose (mg/dL)×fasting insulin (μU/ml) / 405. ***Results:*** A significant reduction in insulin level was observed in intervention group at the end of the study (p=0.003). TC and LDL-C decreased significantly at the end of the study (p=0.016, p=0.009, respectively). Changes in HDL-C, TG and HOMA-IR were not apparent. Surprisingly, FBS increased in the intervention group but it was not statistically significant (p=0.142).***Conclusion:*** Supplementation of type 2 diabetic patients with *Anethum* had beneficial effects on insulin sensitivity and some lipid profiles. Further scientific efforts with large sample size needed to confirm these results.

Introduction

Along with cancer, cardiovascular and cerebrovascular diseases, Diabetes mellitus (DM), is one of the most challenging diseases facing health care professionals today.[1] There was approximately 194 million adults with diabetes mellitus (between 29-79 years old) in 2003 worldwide and it is estimated that it will be increased to more than 333 million in 2030.[2] In 2008 the prevalence of diabetes has been reported 7.7% in Iran.[3]

Obesity, impaired insulin action, insulin secretory dysfunction and increased endogenous glucose output are the major and important characteristics of type 2 diabetic patients[4]. Lipid abnormalities can be observed in type 2 diabetes mellitus[5]. According to the previous studies, there was a relationship between lipid abnormality and insulin resistance in type 2 diabetes mellitus. [6,8]

Although, it seems that type 2 diabetes mellitus is a multifactorial disorder, it has been strongly established that diet can play a major role in the incidence and progression of the disease.[9] Considering many harmful side effects of long-term consumption of drugs, use of complementary and alternative medications seems logical and effective approach to prevent or treat different abnormalities in type 2 DM.[10]

Anethum Graveolens L, known as Dill, is one of the most common herbs with a long history of applying as a remedy and spices in foods[11,12]. This herb is an annual herb, belongs to Apiaceae family[13]. It is growing in the Mediterranean region, Europe, central, southern Asia and widely cultured in southeastern region of Iran.[12]

All segments of freshly plant including stem, leaves, seed and fruit are widely used as condiment in foods and in various medicinal productions.[11] *Anethum* leaves are a source of minerals, proteins and fibers.[14] Anethoferon, carvone and limonene are the most important components of *Anethum* oil with various biological roles.[15]

Beside many beneficial effects of *Anethum Graveolens* including anti-cancer, anti-spasmodic, anti-hypolipidemic and anti-hypercholesterolemic, it prevents colic (in babies), improves some upper

***Corresponding Author:** : Laleh Payahoo, Student Research Committee, Department of Nutrition, Faculty of Health and Nutrition, Tabriz University of Medical Science, Tabriz, Iran. Tell: +98 411 3357581, Email: lllpayahoo44@gmail.com

respiratory system diseases and it has galactagogue (during nursing mothers)[16], antimicrobial[17,18] and anti-inflammatory effects.[19,20] Little attention has been paid to evaluate the effect of *Anethum Graveolens* on insulin sensitivity and blood biochemical parameters in type 2 diabetic patients. Therefore, this study was designed to investigate the effects of *Anethum* Graveolens supplementation on the insulin sensitivity; fasting blood glucose and lipid profile in type 2 diabetic patients.

Methods:

This randomized, double blind, placebo-controlled study was conducted on 60 type 2 diabetic patients. Subjects ere recruited from diabetes association in Tabriz, Iran between January to March in 2012. The local ethics committee of Tabriz University of Medical Sciences approved the research protocol by the number of 9043. Exclusion criteria of the study were insulin therapy at the onset or during the study, smoking and use of alcohol, pregnant and breastfeeding women, consumption of *Anethum* and other herbal supplements, antioxidants, during 3 month ago, presence of acute and chronic diseases including kidney, liver, cardiovascular and gastrointestinal diseases. After explanation of nature of study, finally a written informed consent was taken from all participants with the ages between 18-65 years.

Sample size was determined based on data from previous study.[20] By considering the confidence interval of 95%, $\alpha = 0.05$ and power of 80%, using formula $N= [(Z1-\alpha/2 + Z1-B)^2 (SD_1^2+SD_2^2)] /\Delta^2$, 25 diabetic patients were considered for each group. Regarding to a possible loss in follow-up period, a margin of 20% was determined, and finally 30 patients were allocated in each group.

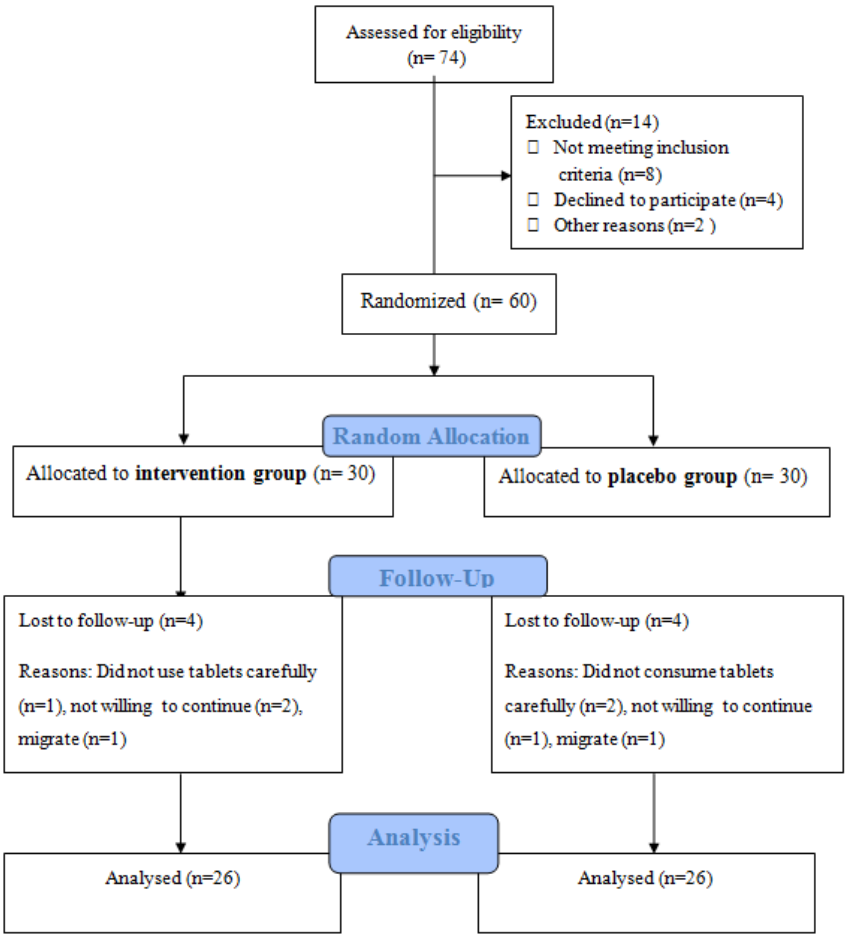

Figure 1. Diagram of how to recruit the type 2 diabetic patients during the study

Tablets preparation

Fresh and green Anethum Graveolens herbs (leaves, stems) were purchased from local market and after washing were dried to make powders. The powders were delivered to a pharmaceutical lab (Tabriz university of medical science, Iran) to prepare tablets containing 1.1 gr powder of Anethum in each one. Starch was used to make placebo. The color and shape of Anethum and placebo tablets were similar with together. A third

person who was not directly involved in the study placed tablets in the same bottles. This person labeled the bottles with 2 cods which retained unknown for researchers until the end of intervention. To evaluate the compliance of patients, participants who consumed more than 90% of tablets were included in statistically analysis and bottles containing tablets were given monthly.

Seventy four diabetic patients were candidate and finally 60 eligible patients were selected to take part in this study. These 60 patients were randomly divided to intervention (n=30) and placebo group (n=30) based on a random block procedure produced by Random Allocation Software (RAS).[21] Intervention group received one tablet of Anethum after each meal (breakfast, lunch and dinner) and placebo group received the same amount starch for 8 weeks. Participants were asked to continue their usual diet and medications according to physician prescription. During the study, 8 patients did not complete the study and data analysis were done on 52 patients (26 in each group) who carefully completed follow-up period and protocol of study. Figure 1 display the protocol of study.

Anthropometric measurements including weight, height, waist and hip circumference were done at the baseline and after intervention. The body weights were measured without shoes and light clothing by a Seca scale (Seca, Hamburg, Germany). Heights were also measured using a stadiometer (Seca) without shoes. BMI was calculated (weight in kilogram divided by the square of the height in meter). Waist and hip circumference was measured with a non-elastic tape.

Blood samples (5cc) were collected at the beginning and at the end of 8 weeks after 10-12hr fasting state and the serum samples were obtained by high-speed centrifugation at least 10 minute and were frozen immediately at −70°C until assay. Serum concentration of FBS, TG, TC, LDL-C and HDL was determined by enzymatic colorimetric method (Parsazmun and Shimatso kits) (Abbott, model Alcyon 300, USA). Serum insulin concentration was determined by ELISA method. Insulin resistance was estimated according to the Homeostasis Model Assessment (HOMA) calculated as: HOMA-IR = fasting concentrations of glucose (mg/dL) × fasting insulin (μU/mL) / 405.[22]

Statistical analysis

The data were analyzed by SPSS software (version 13.0; SPSS Inc, Chicago, IL). Normality of data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±SD and qualitative data were presented as frequency (percentage).Paired t-test was used to compare the differences within group before and after the supplementation. Analysis of covariance (ANCOVA) was used for the comparison of post treatment values of variables after adjusting for baseline values and confounding variables (age, gender, type of consumed hypoglycemic drug and use of hypolipidemic drugs) between groups. In addition, Chi-square test was examined the differences in gender variable in both groups. P value less than 0.05 considered statistically significant.

Table 1. Demographic characteristics of participates in the onset of the study (n=52)

Variables	Intervention group (N=26)	Placebo group (N=26)	P*
Age (year) [Mean(SD)]	53.11±7.23	53.11±7.93	1.000
Gender (N (%))			
Male	11(42.3)	13(50.0)	0.582
Weight (Kg) Mean(SD)	74.13±12.83	79.38±16.97	0.214
BMI (Kg/m^2) Mean(SD)	28.20±3.93	30.63±5.19	0.062
Waist circumference(cm) Mean(SD)	96.53±10.78	100.92±11.22	0.157
Hip circumference (cm)	107.73±8.64	108.73±8.63	0.678

*Independent t-test

Results

The mean age of participated patients was 53.11±7.51 years. No statistically significant differences observed between genders and other variables including age and anthropometric measurements at baseline.

Table 1 shows demographic characteristics of participants in the onset of study.

Table 2 depicted the results of biochemical markers (Insulin, HOMA-IR, FBS, TG, TC, LDL-C, HDL-C) at baseline and at the end of study in both groups. Total cholesterol and LDL-C decreased significantly in intervention group at the end of the study (p=0.016 and p=0.009 respectively). However, these results did not approve after adjusting for baseline and confounding variables by AVCOVA test (p=0.191, p=0.089 respectively). Regarding other lipid profile markers (TG and LDL-C), the results manifested any significant changes in intervention group. Surprisingly, FBS increased slightly and non-significant in intervention group (p=0.142).

Insulin concentration decreased in intervention group significantly (p=0.003). This result also confirmed by

ANCOVA test after adjusting for baseline and confounding variables (p=0.001). HOMA index increased slightly due to the effects of increased FBS.

Table2: The results of biochemical markers in baseline and at the end of the study in intervention and placebo groups (n=52)

Variables	Intervention group (N=26)		p^a	PC Lower to upper	Placebo group (N=26)		p^a	PC Lower to upper	p^b
	Baseline	After			Baseline	After			
Insulin (μU/ml)	11.59±2.66	10.47±2.73	0.003*	-15±24, -2.64	11.86±3.21	12.55±3.47	0.150	-1.17±16.67	0.001*
FBS (mg/dl)	141.07±44.02	155.42±60.90	0.142	-0.42,26.67	141.26±44.20	164.38±48.95	0.005*	6.82,31.85	0.732
HOMA-IR	3.98±1.80	4.04±1.87	0.833	-10.21, 23.60	4.14±1.93	5.13±2.39	0.005*	11.71,46.40	0.075
TG (mg/dl)	148.76±58.86	136.76±69.72	0.361	-15.45,3.55	120.38±48.72	155.11±57.60	0.006*	-2.70,37.11	0.072
TC (mg/dl)	152.76±30.09	129.84±37.19	0.016*	-24.00,-0.24	152.50±37.32	144.96±44.79	0.472	-12.91,9.90	0.191
LDL-C (mg/dl)	87.07±20.19	71.57±23.08	0.009*	-28.48,0.98	91.23±21.10	84.65±6.12	0.119	-15.07,2.06	0.089
HDL-C (mg/dl)	45.42±8.77	42.80±7.75	0.164	-11.50,4.17	45.65±6.56	43.88±6.56	0.250	-9.87,5.08	0.682

*statistically significant, p^a Paired t-test, p^b: ANCOVA test between two groups with adjusting for baseline values and confounding variables (age, gender, type of consumed hypoglycemic drug, use of hypolipidemic drugs) PC: Percent Changes

Discussion

Type 2 DM is a heterogeneous metabolic disorder characterized by the impairment of insulin secretion from pancreatic β-cells, insulin resistance in peripheral tissues and lipid abnormality.[23,24] The use of herbs for treatment or prevention of insulin resistance in diabetic patients has been common, recently. Cinnamon and Cortidis Rhizoma are examples of herbs recognized for insulin secretagogues effects.[25,26]

In present study, insulin concentration decreased significantly at the end of the study. It was shown that green vegetables such as Anethum are rich in antioxidant components including vitamin C, polyphenols and carotenoieds.[27,29] Reactive oxygen species (ROS) are associated with the inflammatory response and oxidative stress as other complication of type 2 DM.[30,31] Beside the neutralizer of ROS properties of antioxidant and flavonoid components of Anethum, these components can be involved in repairing of damaged β-cells and insulin secretion.[32-34]

Supplementation of Anethum resulted in significant reduction in serum total cholesterol and LDL-C concentration, however, no obvious changes were observed in serum triglyceride and HDL-C level. Several human and experimental studies reported controversial results about the effect of Anethum on lipid profile biomarkers. Hajhashemi and Abbasi[35], showed that supplementation of 16 hypercholesterolemic wistar male rats with 10% Anethum powder for 2 weeks resulted in a significant reduction in TC, LDL-C and TG and a significant increasing in HDL-C levels. In Madani et al,[34] survey, fifteen male rats in three five group, were used to supplementation with dill extract for 48 hours. The control group, received physiological serum, diabetic control group (DCG), diabetes was induced using Alloxan monohydrate at a dose of 120 mg/kgbw and the the treated diabetic control group (TDCG) rats were dosed with 300 mg/kg/w hydroalcoholic Anethum graveolens extract. The results indicated significant reduction in glucose, total cholesterol, triglyceride, LDL and VLDL levels in TDCG rats compared to DCG rats. Due to the use of dill extract, HDL level was significantly increased. In other study yazdanparast et al.,[12] displayed that supplementation of 18 male rats in three groups normal diet, high fat diet and high fat diet with 1 mg Anethum extract equivalent 500 mg of the plant powder for up to 10 and/or 30 day decreased serum TC, TG and LDL-C compared to rats which were fed high fat diet, and the concentration of serum HDL-C increased significantly after 30 days. In contrast, Kojuri et al.,[36] represented 650 mg Anethum supplementation in hyperlipidemic patients twice daily for six weeks, have significant changes on the mean TC and LDL-C. However, triglyceride level increased and HDL-C reduced.

The possible underlying mechanism by which Anethum can exert its lipid lowering activities is not completely elucidated. However, several fundamental effective mechanisms have been proposed: a) phenolic components mainly flavonoids in Anethum graveolens that can modify LDL/HDL ratio [12], b) increasing LDL receptors and uptake of LDL and inhibition the activity of acetyl-CoA carboxylase[37] c) reduction in cholesterol absorption from intestine by binding to bile acids 4) decreasing HMG-COA reductase activity and suppression cholesterol and fatty acids synthesis. [12]

Fasting blood glucose increased slightly after

intervention in our study. In agreement of our findings, Piri et al,[38] demonstrated the supplementation of diabetic and normal rats (88 Wistar male rats) which were fed high fat diet with Anethum extract (50, 100, 200 mg/kg) for 3 weeks increased significantly plasma blood glucose in diabetic rats compared with normal rats in a dose-dependent manner ($p<0.001$). In contrast, Madani et al,.[34] investigation showed a significant reduction in blood glucose with supplementation of male diabetic rats with receiving 300 mg/kg/w hydroalcoholic extract of Anethum graveolens for 10 day (200-250g). It was reported that Anethum has some kind of coumarin components with phototoxicity effects that can aggravate oxidative stress and encourage destruction on β-cells that have role in increasing endogenous glucose output.[39,40]

Conclusion

To the best of our knowledge, this was the first study investigated the effect of Anethum graveolens supplementation on the insulin sensitivity and fasting blood glucose, insulin resistance index (HOMA) and lipid profile biomarkers in type 2 diabetic patients. The results showed an improving in the insulin sensitivity as a major complication of type 2 diabetes. Moreover total cholesterol and LDL-C concentration deceased significantly at the end of study in supplemented group; however, fasting blood glucose, HDL-C, triglyceride and HOMA index did not change significantly. Regarding to the novelty and preliminary nature of this study, further scientific efforts with large sample size and in safe dose of Anethum are certainly needed to confirm our results.

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