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# The effects of Anethum graveolens (dill) powder supplementation on clinical and metabolic status in patients with type 2 diabetes

**Fatemeh Haidari**
Ahvaz Jondishapour University of Medical Sciences
**Mehrnoosh Zakerkish**
Ahvaz Jondishapour University of Medical Sciences
**Fatemeh Borazjani**
Ahvaz Jondishapour University of Medical Sciences
**Kambiz Ahmadi Angali**
Ahvaz Jondishapour University of Medical Sciences
**Golnaz Amoochi** ( golnazamoochi@gmail.com )
Ahvaz Jondishapour University of Medical Sciences

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# Abstract

Background: The objective of this study was to investigate the effects of anethum graveolens (dill) powder supplementation on glycemic control, lipid profile, some antioxidants and inflammatory markers, and gastrointestinal symptoms in type 2 diabetic patients. Material and methods: In this study, 42 patients with type 2 diabetes were randomly allocated to intervention and control groups and received either 3g/day dill powder or placebo (3 capsules/day, 1 g each). Fasting blood sugar (FBS), insulin, homeostatic model assessment of insulin resistance (HOMA- IR), lipid profile, hs-C-reactive protein (hs-CRP), total antioxidant capacity (TAC), malondialdehyde (MDA), and gastrointestinal symptoms were measured in all of the subjects at baseline and post-intervention. Results: The dill powder supplementation significantly decreased the mean serum levels of insulin, HOMA-IR, LDL-C, TC, and MDA in the intervention group in comparison with the baseline measurements ($p < 0.05$). Also, the mean serum levels of HDL and TAC were significantly increased in the intervention group in comparison with the baseline measurement ($p < 0.05$). Colonic motility disorder was the only gastrointestinal symptom whose frequency was significantly reduced by supplementation ($P = 0.01$). The mean changes of insulin, LDL-C , TC, and MDA were significantly lower in the intervention group than in the control group ($p < 0.05$). In addition, the mean changes in HDL were significantly higher in the intervention group than in the control group ($p < 0.05$). Conclusion: Dill powder supplementation can be effective in controlling the glycemic, lipid, stress oxidative, and gastrointestinal symptoms in type 2 diabetic patients. Keywords: Type 2 diabetes; Dill powder; Glycemic control; Lipid profile; Stress oxidative status


# Introduction

Diabetes is a public health problem that affected 285 million adults in 2010. That number is expected to rise to 439 million—or 7.7% of all adults—by 2030 (1). In Iran, it has been estimated that 8% of the adult population has diabetes (2). Major characteristics of type 2 diabetes mellitus (T2DM) are obesity, impaired insulin action, insulin secretory dysfunction, and increased endogenous glucose output (3). Increased free fatty acid flux secondary to insulin resistance is associated with diabetic dyslipidemia, including high plasma triglyceride concentration and low HDL cholesterol concentration (4). Inflammatory cytokines contribute to T2DM occurrence by affecting beta-cell function, which, in turn, promotes the long-term complications of diabetes by intensifying hyperglycemia (5). Increased glucose uptake by endothelial cells in hyperglycemic conditions also leads to the increased production of free radicals, which decreases antioxidant levels (6). It is commonly reported that patients with T2DM also encounter gastrointestinal complications, including gastroesophageal reflux disease (GERD), gastroparesis, enteropathy, nonalcoholic fatty liver disease (NAFLD), and glycogenic hepatopathy (7).

Anethum graveolens L (commonly referred to as dill), is a herb commonly used both as a remedy and as a spice (8). It grows in the Mediterranean region, Europe, central and southern Asia, and the southeastern region of Iran (9). *Anethum graveolens* (AG) leaves are a source of minerals, proteins, and fibres (10). AG oils are also a source of antioxidants and have antimicrobial and antispasmodic properties (11). In traditional herbal medicine, AG is used to treat gastrointestinal ailments such as indigestion and

flatulence (12). AG has been established to have anticancer, antimicrobial, antigastric irritation, anti-inflammatory, and antioxidant properties (13). In diabetic models, the administration of different extractions of AG seed had antioxidant, hypolipidemic, and hypoglycemic effects (14).

Earlier studies have reported inconsistent findings regarding the protective effects of AG on lipid profile and insulin resistance in patients with metabolic syndrome (15, 16). Randomized clinical trials showed that AG reduced total cholesterol and low-density lipoprotein cholesterol (LDL-C) but did not change triglyceride and high-density lipoprotein cholesterol (HDL-C) in patients with T2DM (17). It has also been reported that AG could have beneficial effects on some inflammatory biomarkers (18) and controversial effects on glucose and insulin (18, 19). Given the inconclusive results related to glycemic, lipid and inflammatory profiles, it is not clear whether AG helps to increase antioxidants or improve gastrointestinal symptoms. Therefore, the present study was designed to examine the effects of AG powder on the serum levels of glycemic parameters, lipid profile, some antioxidants, inflammatory markers, and gastrointestinal symptoms in patients with type 2 diabetes.

# Materials And Methods

### Study design and participants

A single-centre randomized double-blind placebo-controlled study was conducted with 100 type 2 diabetes patients. The patients were recruited from the endocrinology and metabolism clinics of Golestan Hospital at Ahvaz Jundishapur University of Medical Science in Iran between 2017 and 2018 (Fig. 1).

Inclusion criteria: patient has DM; is aged 30-60 years; has gastrointestinal symptoms; has a body mass index (BMI) between 25 and 35 kg/$m^2$; does not have systemic diseases, thyroid disease, or kidney disorder; is not pregnant or lactating; and is not taking any dietary supplements or antioxidants, immunosuppressants, or anti-inflammatory agents. Exclusion criteria: patient shows noticeable changes in the dose of medications and treatment of diabetes, refuses to continue participating in the study, or has less than 90% compliance with dill capsules.

Diagnosis of DM was done according to American Diabetes Association guidelines. Patients with FBS ≥ 126 mg/dl or (2-hour glucose) 2 hpp ≥ 200 mg/dl, or HbA1c ≥ 6.5% were diagnosed with diabetes mellitus (20).

Fifty-two patients did not qualify for this study due the not meeting inclusion criteria such as gastrointestinal symptoms and not accepting to participate. Forty-eight patients were randomly assigned to two groups of intervention ($n$ = 24) or placebo ($n$ = 24), for 8 weeks. Randomization was done using the computer-generated random numbers by a third person to reduce the bias. The third person were generated a random block in blocks of 4. The naming of Dill or placebo bottles were done according to random numbers. Odd or even numbers were allocated randomly to groups A or B. A multi-part questionnaire including demographic data (age and sex), anthropometric indices, dietary intake, medication, diabetes duration (in years), physical activity, and gastrointestinal symptoms was obtained

from the subjects. During each visit, every patient was given dill supplement or placebo for 4 weeks and throughout these weeks, consumption of supplements or placebo by the patients was ensured through phone calls or text messages. The compliance of patients was checked by counting the remaining capsules. Patients were excluded from study if they had consumed less than 90 % of the prescribed capsules. All participants were asked not to consume dill in their diet during the study. The protocol of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.REC.1396.623) and this study was registered in the Iranian Registry of Clinical Trials website (IRCT20120704010181N12) which is available at: http://irct.ir/user/trial/20288/view. Written informed consent was obtained from all participants.

### Supplement and placebo prescription

After confirmation of the Anethum Graveolens (dill) herb by the botanist, dried leaves were milled to powder. Capsules containing 1 g of dill powder were provided by the Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences. In this study, starch was used as placebo. The intervention and control groups received either 3 capsules of 1 gr dill or placebo three times per day after each meal (breakfast, lunch and dinner) for 8 weeks. The placebo and dill capsules were matched with together in terms of size, taste, color and shape.

### Assessment of demographic data, anthropometric indices and food intakes

Dietary intakes were investigated with a 24-h food recall for 3 days (2 weekdays and 1 weekend day), and dietary intake was analyzed by Nutritionist 4 software specified for Iranian foods. Aanthropometric indices (weight, height, BMI) were measured by a trained researcher (nutritionist) at baseline and after the 8-week intervention. Weight (Seca, Germany) was measured while the patients wore light clothing and no shoes with 0.1-kg accuracy for weight. Height was measured using a stadiometer (Seca) with 0.5-cm accuracy without shoes. BMI was calculated (weight in kilogram divided by the square of the height in meter). Physical activity level was evaluated by the Persian form of the International Physical Activity Questionnaire (IPAQ) and presented in Met-Min/week. The participants were asked not to change their ordinary dietary intake and physical activity during the intervention.

### Assessment of gastrointestinal symptoms

The assessment of gastrointestinal symptoms was done by questionnaire at the baseline and end of the study (21). This questionnaire was included gastrointestinal symptoms such as gastroesophageal reflux, esophageal motility disorders, dyspepsia, gastric motility disorders and colonic motility disorders.

The numbers 0, 1 and 2 indicate the severity of gastrointestinal symptoms. 0: the patient did not have gastrointestinal symptoms, 1: patient had occasional gastrointestinal symptoms, and 2 ≤: the patient had permanently gastrointestinal problems.

### Biochemical assays

Fasting blood samples (5 ml) were collected from all participants at the beginning and end of the study and were immediately centrifuged (3000×g, 10 min, 4ºC). Blood samples were poured into anticoagulant tubes in order to extract serum samples and sent to the lab in cool boxes. All samples were stored at − 70 °C until biochemical analyses. Serum glucose, TG, HDL and TC was measured by the standard enzymatic methods using Pars Azmoun kit (Tehran, Iran). Serum insulin was measured by human insulin enzyme-linked immunosorbent (ELISA) kit (monobind). 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). Friedewald formula was used for calculation of LDL (23):

LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5 (VLDL), VLDL =TG (mg/dl)/5

Serum markers of oxidative stress such as total antioxidant capacity (TAC) and malondialdehyde (MDA) were measured by reliable spectrophotometric methods using Zell Bio GmbH kit (Germany). Serum levels of hc-CRP were measured by enzyme-linked immunosorbent assay (ELISA) kits (Diagnostics monobind).

### Outcomes

In this study, LDL-C was considered as the primary outcome. Also, the secondary measurements outcomes were glycemic parameters, other factors of lipid profile, some antioxidant and inflammatory markers, and gastrointestinal symptoms.

### Statistical analysis

The sample size (95% confidence interval and 80% power) was computed according to Mobasseri and et al study (17) and considering LDL-C as the main outcome. Sample size was 21 subjects for each group. 24 subjects were computed in each group with 10% withdrawal. All statistical analyses was performed using SPSS 25. All data were reported as mean ± standard deviations (SD) for quantitative variables or number (percentage) for qualitative variables. Normal distribution of data was checked using Kolmogorove-Smirnov test. Paired sample t-test was also used to compare the results within groups post-intervention. Independent sample t-test was performed to compare the results between the two groups (placebo and intervention). Also, Independent T-test was used to identify differences between the two groups at the end of the study. The mean changes of variables was calculated using the mean differences of data before and after the study. Analysis of covariance (ANCOVA) was used to identify any differences between two groups at the end of the study, adjusting for baseline values and covariates. Also, Chi square test was used for statistical analysis of qualitative variables. P-value of less than 0.05 was considered statistically significant in all analyses.

# Results

### Baseline characteristics of the subjects, anthropometric parameters and dietary intake

42 diabetic patients (intervention group n = 21; control group = 21) for 8 weeks completed the study. The mean age of patients in the intervention and control groups was 50.66 ± 8.22 and 50.42 ± 8.61 years, respectively. No significant differences (P ≥ 0.05) were observed in demographic and anthropometric characteristics, duration of diabetes, physical activity and medications between the two groups at baseline (**Table 1**). No significant differences were also observed between the two groups for dietary intake including energy, macronutrients and micronutrients such as antioxidant vitamins C and E at baseline and after the intervention (P ≥ 0.05) (**Table 2**).

### Glycemic control

The results of this study showed that no significant differences were observed in FBS, insulin and HOMA-IR between 2 groups at baseline (P ≥ 0.05). It was demonstrated that 8 weeks consumption of dill powder significantly decreased the mean serum levels of insulin and HOMA-IR in the intervention group in compare with baseline (13.27± 3.8 vs 10.54 ± 4.51 μU/ml, respectively; P = 0.004), HOMA-IR (4.88 ± 2.37 vs 3.86 ± 2.32, respectively; P = 0.039). Furthermore, the mean changes of insulin was significantly lower in the intervention group in compare with control group after the intervention (-2.7 ± 3.83 vs 0.50 ± 4.36, respectively; P = 0.015). Analysis of covariance (ANCOVA) showed that after the adjusting of confounding factors (age, duration of disease, changes of body mass index, dietary intake of energy, macronutrients, Vitamin A, C, and E, and physical activity), the mean changes of insulin were not significantly (P= 0.05) lower in the intervention group in comparison with control group after the intervention (**Table 3**).

### Lipid profile

At baseline, there were no significant differences in the mean serum levels of TG, TC, LDL-C and HDL between two groups (P > 0.05). The dill powder supplementation significantly increased the mean serum levels of HDL in the intervention group in comparison with baseline (44.80 ± 9.89 to 41.85 ± 11.68 mg/dl, respectively; P = 0.007). Also, the mean changes of serum levels of HDL were significantly higher in the intervention group compared to the control group (2.59 ± 4.51 vs -1.38 ± 4.60 mg/dl, respectively; P = 0.004). Even after the adjusting of confounding factors, there was a significant difference in mean change of HDL-C between two groups (P = 0.04). In the intervention group, it was shown that the mean serum levels of LDL-C and TC significantly decreased post-intervention (81.00 ± 34.79 to 71.23 ± 26.63 mg/dl, respectively; p = 0.029), TC (160.28 ± 38.26 to 149.23 ± 26.7 mg/dl, respectively; p = 0.03). Furthermore, the mean changes of serum levels of LDL-C were significantly lower in the intervention group compared to the control group (-9.76 ± 19.08 vs 3.09 ± 14.07 mg/dl, respectively; P = 0.017). After the adjusting of confounding factors, there was a significant difference in mean change of LDL-C and TC between two groups (P = 0.04 and P= 0.033, respectively). However, no significant changes were observed in the mean serum levels of TG after the intervention (P ≥ 0.05) (**Table 3**).

### Antioxidant and inflammatory markers

According to the analysis, there were no significant differences in the mean serum levels of hs-CRP, MDA and TAC between two intervention and control groups at the baseline (P ≥ 0.05). The results of present study showed that in intervention group the mean of MDA was reduced significantly post-intervention in comparison with baseline (3.34 ± 2.05 to 2.22 ± 1.57 μM, respectively; P = 0.034). At the end of study, there was a significant difference in the mean changes of MDA between intervention and control groups without and with the adjusting of confounding factors (-1.11 ± 2.24 vs 0.33 ± 1.62 μM, respectively; P = 0.021 vs P = 0.013, respectively). Within group comparison in the intervention group showed that the mean serum levels of TAC significantly increased after 8 weeks of supplementation (0.19 ± 0.05 to 0.25 ± 0.09 mM, respectively; p=0.025). In addition, after the supplementation, the mean serum levels of TAC were significantly higher in the intervention group in comparison with the control group (0.25 ± 0.09 vs 0.16 ± 0.06 mg/dl, respectively; P = 0.001). This result for TAC was also observed after the adjusting of confounding factors (P = 0.004). No significant difference was observed for hs-CRP within and between the two groups (P ≥ 0.05) **(Table 4)**.

### Gastrointestinal symptoms

Based on the results presented in Table 5, supplementation with dill failed to reduce the frequency of gastrointestinal symptoms such as gastroesophageal reflux, esophageal motility, dyspepsia, and gastric motility disorders in comparison with the baseline measurements (P ≥ 0.05). Amongst all the symptoms, only colonic motility disorders had their frequency significantly reduced by supplementation (P = 0.01), and this decrease was more notable in patients with severe gastrointestinal problems. In the control group, meanwhile, there was no significant reduction in the frequency of gastrointestinal symptoms (P ≥ 0.05).

### Safety, adverse effects and monitoring data

A Data Monitoring Committee (DMC) was supervised this study to detect any possible side effects and report to the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. However, no significant side effects from dill administration were reported in this study.

## Discussion

This study revealed that 8 weeks of supplementation with 3 g/day AG reduced serum insulin and HOMA-IR. Moreover, AG might significantly reduce the serum levels of LDL and TC and enhance HDL when compared to a placebo condition. Patients in the intervention group had low MDA and TAC; however, no significant changes were observed for the serum levels of hs-CRP. In terms of gastrointestinal symptoms, only colonic motility disorders decreased.

These findings are in line with those of several interventional studies confirming the benefits of AG in improving T2DM and metabolic syndrome (14, 16). The significant reduction in HOMA-IR and serum levels of insulin indicates that AG has a role to play in reducing insulin resistance. Similar beneficial effects of AG on glycemic control have been reported previously. Supplementation of T2DM patients with

3.3 g/day of powder of Anethum for 8 weeks could significantly reduce levels of insulin (17). After 6 weeks of supplementation with 1.5g/day of dill powder tablets, serum levels of FBS were significantly reduced in patients with T2DM (19).

Although Payahoo et al. (18) found a significant decrease in serum levels of insulin, no significant effect was observed for HOMA-IR, which could be due to the reduced levels of FBS in diabetic patients. High antioxidant content (i.e., vitamin C, polyphenols, and carotenoids) in AG neutralizes reactive oxygen species and thus plays a role in repairing beta-cell function and insulin secretion (24, 25).

In this study, serum concentrations of LDL-C and TC decreased, while HDL-C increased significantly at the end of the study. No significant change was seen for serum levels of TG. In agreement with our study, Rashidlamir et al. (26) showed that aerobic training with the use of 2.7 g/day of AG resulted in increased HDL and a decreased LDL-to-HDL ratio in diabetic women compared with the control group; findings for TC, meanwhile, was not statistically significant. In contrast, supplementation with 650 mg of anethum tablets twice daily increased the serum levels of TG in patients with hyperlipidemia, but no significant changes were seen in TC or LDL (15).

The treatment of hyperlipidemic patients with 1 g/day of AG powder for 4 weeks resulted in a significant reduction in the levels of TC, TG, LDL and VLDL when compared to patients treated with 20 mg/day of lovastatin tablets. However, no significant change was observed in the serum levels of HDL(27).

The exact mechanism of the lipid-lowering effects of AG is not yet determined. However, it may relate to the decreased absorption of cholesterol by binding to bile acids, the inhibition of cholesterol and fatty acid synthesis through the suppression of acetyl-CoA carboxylase and HMG-COA reductase activity and the stimulation of cholesterol clearance by increasing LDL receptors (28-30).

In this study, patients who received 3 g/day of AG had lower levels of MDA and higher levels of TAC than patients in the control group, both in crude and adjusted models. MDA is a product of lipid peroxidation and is recognised as an atherogenic agent. Patients with elevated levels of MDA are more susceptible to atherosclerosis, diabetes, and other metabolic disorders (31).

Findings from animal studies showed that the administration of different fractions of AG to animals on a high-fat diet decreased their MDA levels and increased the activities of antioxidant enzymes, including superoxide dismutase (SOD) and catalase. It also increases the levels of glutathione (GSH), thus playing a key role in scavenging ROS (32). Hamsters treated with AG extracts or tablets exhibited a significant increase in TAC levels when compared to those on a high-cholesterol diet (33). AG is composed of a variety of antioxidants, such as flavonoids—capable of scavenging free radicals (34). The enhanced levels of antioxidant activity in response to AG might be due to the content of polyphenols and flavonoids. It’s possible that  normal levels of antioxidants protect individuals against several chronic diseases (35).

We observed a non-significant decrease in serum levels of hs-CRP after supplementation with AG. The fact that an increase in body weight is an indicator of inflammation (36) could be why a non-significant reduction in serum levels of hs-CRP was observed in our study. The anti-inflammatory effects of different forms of AG have been shown in several animal studies (37-39). Payahoo et al. (18) found a significant decrease in the serum levels of inflammatory biomarkers—including hs-CRP, IL-6, and TNF-α—after 8 weeks of supplementation with 3.3 grams of dill powder.

In terms of gastrointestinal symptoms, we observed a significant decrease in colonic motility disorders only. It is reported that the most prevalent symptoms among diabetic patients are colonic motility disorders, which increase with age (21). The prevalence of gastrointestinal symptoms is positively associated with the duration of diabetes (21, 40). Patients included in the current study had a mean age of 50 years and a mean disease duration of 8 years—both of which are relatively high. This could be a reason for the observed findings in this regard. Earlier animal models show that AG extract is a potent relaxant of contractions in rat ileum and has antisecretory and anti-ulcer capabilities as it relates to HCl- and ethanol-induced stomach lesions (41, 42).

To the best of our knowledge, this is the first human study investigating the effects of AG on gastrointestinal symptoms. The major strength of this study was its design as a well-controlled double-blind clinical trial that controlled for several main confounding factors in different models.

However, there are some limitations to our study. First, this is a single-dose trial, thus preventing any dose-effect associations. It remains unclear whether larger or smaller doses could introduce a stronger clinical effect. Second, the narrow range of inclusion criteria led to unrepresentative samples, therefore limiting the generalizability of the study results to all diabetic patients. Third, only the data of subjects who completed the study were analyzed; the data of those who were excluded were not measured.

# Conclusion

In conclusion, the present study suggests beneficial effects of AG in insulin resistance, LDL and HDL cholesterol, antioxidant levels, and some gastrointestinal symptoms compared with placebo during 8 weeks of supplementation. Further studies are needed to determine molecular levels and clarify its role in the treatment of diabetes complications.

# Abbreviations

Fasting blood sugar (FBS), gastro-esophageal reflux disease (GERD), high-density lipoprotein (HDL), homeostatic model assessment of insulin resistance (HOMA-IR), hs-C-reactive protein (hs-CRP), low-density lipoprotein (LDL), malondialdehyde (MDA), non-alcoholic fatty liver disease (NAFLD), total antioxidant capacity (TAC), total cholesterol (TC), triglyceride (TG).

# Declarations

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### Author contribution

Amoochi G, Haidari F concepted the idea and designed the study. Amoochi G and Zakerkish M collected the data. Haidari F and Ahmadi Angali K analyzed and interpreted the results. Amoochi G, Haidari F and Borazjani F drafted the manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

The results will not be available before publishing.

### Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.REC.1396.623) that is in accordance with the Declaration of Helsinki. Each participant will sign an informed consent form.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

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# Tables

Table 1 Demographic and anthropometric characteristics of participants at the baseline and at the end of the study.

| Variable | Dill powder (n=21) | Placebo (n=21) | *P-value |
|---|---|---|---|
| Age (year) | 50.66 ± 8.22 | 50.42 ± 8.61 | 0.927 |
| Gender*** | | | |
| Female | 14 (66.7%) | 16 (76.2%) | 0.495 |
| Male | 7 (33.3%) | 5 (23.8%) | |
| Duration of disease (year) | 8.1 ± 5.49 | 8.57 ± 6.72 | 0.714 |
| Weight (kg) | | | |
| Baseline | 78.22 ± 11.08 | 77.29 ± 8.42 | 0.761 |
| End | 78.08 ± 11.07 | 77.30 ± 8.25 | 0.796 |
| P-value** | 0.602 | 0.987 | |
| BMI | | | |
| Baseline | 29.42 ± 3.24 | 28.95 ± 1.94 | 0.753 |
| End | 29.37± 3.29 | 28.95 ± 1.90 | 0.725 |
| P-value** | 0.627 | 0.904 | |
| min/week)-Physical activity (MET | | | |
| Baseline | 1314.33 ± 1036.19 | 1428.66 ± 1053.76 | 0.725 |
| End | 1254.33 ± 960.52 | 1495.66 ± 953.10 | 0.419 |
| P-value** | 0.626 | 0.451 | |

Values are expressed as means ± SD. *P <0.05* was considered as significant. *P <0.05 was considered as significant using Mann–Whitney U (for duration of disease and BMI) and Independent T-test (for other variables) between the two groups at baseline and after the intervention). ** *P <0.05* was considered as significant using Wilcoxon Signed Ranks Test (for BMI) and Paired T- test (for other variables). ****P <0.05* was considered as significant using chi-square test.

Table 2. Mean ± SD of energy, macronutrients and micronutrients intake at baseline and post-intervention

| Variables | Dill powder (n=21) | Placebo (n=21) | *P-Value* [1] | *P value* [2] |
|---|---|---|---|---|
| **Energy (kcal)** | | | | |
| Baseline | 1881 ± 161 | 1796 ± 167 | 0.100 | 0.113 |
| End | 1861 ± 176 | 1811 ± 163 | 0.339 | 0.257 |
| *P-Value* [3] | 0.412 | 0.593 | | |
| **Carbohydrate(gr)** | | | | |
| Baseline | 249.61 ± 23.19 | 240.40 ± 20.46 | 0.180 | 0.146 |
| End | 246.51 ± 23.61 | 238.23 ± 14.28 | 0.179 | 0.113 |
| *P-Value* [3] | 0.270 | 0.536 | | |
| **Protein (gr)** | | | | |
| Baseline | 75.41 ± 6.15 | 73.43 ± 6.09 | 0.303 | 0.240 |
| End | 74.61 ± 5.72 | 72.04 ± 6.65 | 0.187 | 0.145 |
| *P-Value* [3] | 0.210 | 0.135 | | |
| **Fat (gr)** | | | | |
| Baseline | 61.53 ± 5.37 | 59.66 ± 4.74 | 0.241 | 0.196 |
| End | 60.26 ± 6.24 | 61.93 ± 4.32 | 0.169 | 0.098 |
| *P-Value* [3] | 0.147 | 0.113 | | |
| **Vitamin A (U)** | | | | |
| Baseline | 377.38 ± 103.76 | 321.32 ± 85.71 | 0.064 | **0.034*** |
| End | 368.66 ± 115.02 | 352.93 ± 88.03 | 0.622 | 0.693 |
| *P-Value* [3] | 0.779 | 0.159 | | |
| **Vitamin C (mg)** | | | | |
| Baseline | 87.03 ± 27.87 | 91.36 ± 29.58 | 0.628 | 0.744 |
| End | 91.44 ± 30.92 | 96.85 ± 32.20 | 0.582 | 0.633 |
| *P-Value* [3] | 0.592 | 0.541 | | |
| **Vitamin E (mg)** | | | | |
| Baseline | 2.03 ± 0.72 | 2.38 ± 0.85 | 0.166 | 0.205 |
| End | 1.85 ± 0.52 | 2.12 ± 0.63 | 0.146 | 0.136 |
| *P-Value* [3] | 0.171 | 0.095 | | |

Values are expressed as means ± SD. *P <0.05* was considered as significant.

***P-Value1***: Between group comparison of variables at baseline and after intervention resulted from Independent T-test (for all variables).

***P-Value2***: Between group comparison of variables at baseline and after intervention resulted from Analysis of Covariance (Ancova) in the adjusted models (adjusted for age, duration of disease, and body mass index).

***P-Value3***: Within group comparison of variables resulted from paired sample t test (for all variables)

Table 3. Serum levels of glycemic parameters and lipid profile at baseline and post-intervention.

| Variables | Dill powder (n=21) | Placebo (n=21) | *P-Value* [1] | *P-Value* [2] | *P-Value* [3] | *P-Value* [4] |
|---|---|---|---|---|---|---|
| **FBS** (mg/dl) | | | | | | |
| Baseline | 145.76 ± 50.81 | 148.61 ±56.56 | 0.864 | 0.883 | | |
| End | 141.14 ± 40.37 | 154.23 ±36.72 | 0.278 | 0.623 | | |
| *P-value* [5] | 0.668 | 0.671 | | | | |
| Difference | -4.61± 48.56 | 5.61± 59.76 | | | 0.17 | 0.752 |
| **Insulin** (µU/ml) | | | | | | |
| Baseline | 13.27± 3.8 | 11.61 ± 4.91 | 0.230 | 0.474 | | |
| End | 10.54± 4.51 | 12.12 ± 4.23 | 0.250 | 0.796 | | |
| *P-value* [5] | **0.004*** | 0.604 | | | | |
| Difference | -2.7 ± 3.83 | 0.50 ± 4.36 | | | **0.015*** | 0.05 |
| **HOMA-IR** | | | | | | |
| Baseline | 4.88 ± 2.37 | 4.37 ± 3.01 | 0.544 | 0.762 | | |
| End | 3.86 ± 2.32 | 4.60 ±2.02 | 0.276 | 0.848 | | |
| *P-value* [5] | **0.039*** | 0.698 | | | | |
| Difference | -1.02 ± 2.12 | 0.23 ± 2.68 | | | 0.101 | 0.447 |
| **TG** (mg/dl) | | | | | | |
| Baseline | 196.52 ± 60.16 | 194.66 ± 75.58 | 0.930 | 0.626 | | |
| End | 172.38 ± 69.86 | 190.19 ± 79.93 | 0.447 | 0.664 | | |
| *P-value* [5] | 0.055 | 0.811 | | | | |
| Difference | -24.14 ± 54.29 | -4.47± 84.69 | | | 0.376 | 0.343 |
| **TC** (mg/dl) | | | | | | |
| Baseline | 160.28 ± 38.26 | 154.42 ± 32.42 | 0.596 | 0.492 | | |
| End | 149.23 ± 26.7 | 156.8 ± 32.25 | 0.412 | 0.881 | | |
| *P-value* [5] | **0.03*** | 0.654 | | | | |
| Difference | -11.04 ± 21.7 | 2.38 ± 23.95 | | | 0.064 | **0.033*** |
| **LDL-C** (mg/dl) | | | | | | |
| Baseline | 81.00 ± 34.79 | 71.71 ± 23.55 | 0.318 | 0.516 | | |
| End | 71.23 ± 26.63 | 74.80 ± 22.80 | 0.643 | 0.357 | | |
| *P-value* [5] | **0.029*** | 0.325 | | | | |
| Difference | -9.76 ± 19.08 | 3.09 ± 14.07 | | | **0.017*** | **0.04*** |
| **HDL-C** (mg/dl) | | | | | | |
| Baseline | 41.85 ± 11.68 | 43.14 ± 8.05 | 0.680 | 0.939 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| End | 44.80 ± 9.89 | 41.76 ± 6.33 | 0.243 | 0.343 | | |
| *P-value* [5] | **0.007*** | 0.185 | | | | |
| Difference | 2.59 ± 4.51 | -1.38 ± 4.60 | | | **0.004*** | **0.04*** |

Values are expressed as means ± SD. *Statistically significant. ***P-Value1***: Between-group comparison of variables at baseline and after intervention, resulted from Independent T-test (for all variables).
***P-Value2***: Between-group comparison of variables at baseline and after intervention, resulted from Analysis of Covariance (Ancova) in the adjusted models (adjusted for age, duration of disease, dietary intake of energy, macronutrients, antioxidant vitamins such as vitamins A, C, and E, physical activity, and BMI).
***P-Value3***. Between group comparisons mean Changes of variables resulted from Mann–Whitney U (for FBS) and Independent T-test (for other variables).
***P-Value4***: Between group comparisons mean changes of variables resulted from Analysis of Covariance (Ancova) (adjusted for age, duration of disease, changes of body mass index, dietary intake of energy, macronutrients, Vitamin A, C, and E, and physical activity).
***P-Value5***: Within-group comparison of variables, resulted from Paired T-test (for all variables).
**Abbreviations;** Fasting blood sugar (FBS), homeostatic model assessment of insulin resistance (HOMA-IR), triglyceride (TG), total cholesterol (5), high-density (HDL) and low-density lipoprotein (LDL) cholesterol.

Table 4. The effects of dill supplementation on serum levels of antioxidant and inflammatory markers at baseline and post-intervention

| Variables | Dill powder (n=21) | Placebo (n=21) | *P-Value* [1] | *P-Value* [2] | *P-Value* [3] | *P-Value* [4] |
|---|---|---|---|---|---|---|
| **MDA (µM)** | | | | | | |
| Baseline | 3.34 ± 2.05 | 3.72 ± 2.09 | 0.554 | 0.886 | | |
| End | 2.22 ± 1.57 | 4.06 ± 2.32 | **0.005*** | **0.000*** | | |
| *P-value5* | **0.034*** | 0.354 | | | | |
| Difference | -1.11 ± 2.24 | 0.33 ± 1.62 | | | **0.021*** | **0.013*** |
| **TAC (mM)** | | | | | | |
| Baseline | 0.19 ± 0.05 | 0.17 ± 0.03 | 0.103 | 0.137 | | |
| End | 0.25 ± 0.09 | 0.16 ± 0.06 | **0.001*** | **0.004*** | | |
| *P-value5* | **0.025*** | 0.793 | | | | |
| Difference | 0.058 ± 0.11 | -0.004 ± 0.7 | | | 0.339 | 0.145 |
| **Hs-CRP (mg/L)** | | | | | | |
| Baseline | 4.13 ± 0.84 | 4.29 ± 0.70 | 0.506 | 0.388 | | |
| End | 3.87 ± 0.89 | 4.32 ± 0.93 | 0.122 | 0.143 | | |
| *P-value5* | 0.283 | 0.872 | | | | |
| Difference | -0.25 ± 1.06 | 0.2 ± 0.8 | | | 0.332 | 0.649 |

*Statistically significant. Values are expressed as means ± SD. *P <0.05* was considered as significant.

*P-Value1*: Between-group comparison of variables at baseline and after intervention, resulted from independent sample t-test (for all variables).

*P-Value2*: Between-group comparison of variables at baseline and after intervention, resulted from analysis of covariance in the adjusted models (adjusted for age, duration of disease, dietary intake of energy, macronutrients, antioxidant, vitamins such as vitamins A, C, and E, physical activity, and BMI).

*P-Value3*: Between group comparisons mean changes of variables resulted from Mann–Whitney U (for TAC) and Independent T-test (for other variables).

*P-Value4*: Between group comparisons mean changes of variables resulted from Analysis of Covariance (Ancova) (adjusted for age, duration of disease, changes of body mass index, dietary intake of energy, macronutrients, Vitamin A, C, E, and physical activity).

*P-Value5*: Within-group comparison of variables, resulted from Paired T-test (for all variables).

Abbreviations; Hs-C-reactive protein (hs-CRP), total antioxidant capacity (TAC) and malondialdehyde (MDA)

Table5. The effects of dill powder supplementation on gastrointestinal symptoms at baseline and post-intervention

| Scores | Dill powder (n = 21) | | | Placebo (n= 21) | | |
|---|---|---|---|---|---|---|
| intestinal oms | 0 | 1 | 2 ≤ | 0 | 1 | 2 ≤ |
| esophageal | | | | | | |
| ıe | 5(23.8%) | 7(33.3%) | 9(42.9%) | 7 (33.3%) | 5 (23.8%) | 9 (42.9%) |
| | 6(28.6%) | 9(42.9%) | 6(28.6%) | 7 (33.3%) | 5 (23.8%) | 9 (42.9%) |
| e | | 0.135 | | | 1.00 | |
| ageal motility ers | | | | | | |
| ıe | 18(85.7%) | 1 (4.8%) | 2 (9.5%) | 16(76.2%) | 3 (14.3%) | 2(9.5%) |
| | 16(76.2%) | 3(14.3%) | 2 (9.5%) | 16(76.2%) | 3 (14.3%) | 2(9.5%) |
| e | | 0.317 | | | 1.00 | |
| ɔsia | | | | | | |
| ıe | 15(71.4%) | 2 (9.5%) | 4 (19%) | 14(66.7%) | 3 (14.3%) | 4 (19%) |
| | 12(57.1%) | 7(33.3%) | 2 (9.5%) | 13(61.9%) | 5 (23.8%) | 3 (14.3%) |
| e | | 0.198 | | | 0.368 | |
| c motility ers | | | | | | |
| ıe | 12(57.1%) | 1 (4.8%) | 8(38.1%) | 11(52.4%) | 2 (9.5%) | 8 (38.1%) |
| | 10(71.4%) | 3(14.3%) | 3(14.3%) | 11(52.4%) | 2 (9.5%) | 8 (38.1%) |
| e | | 0.112 | | | 1.00 | |
| c motility ers | | | | | | |
| ıe | 7 (33.3%) | 3(14.3%) | 11(52.4%) | 6 (28.6%) | 5 (23.8%) | 10(47.6%) |
| | 10(47.6%) | 10(47.6%) | 1 (4.8%) | 7 (33.3%) | 4 (19%) | 10 (47.6%) |
| e | | **0.010*** | | | 0.317 | |

*P <0.05* was considered as significant. Data are expressed as Percent of relative frequency of gastrointestinal symptoms. P-value within group comparison of variables resulted from Chi-Square Tests.

The numbers 0, 1 and 2 indicate the severity of gastrointestinal symptoms. 0; the patient hadn't gastrointestinal symptoms, 1; patient had occasional gastrointestinal symptoms. 2 ≤; the patient had permanently gastrointestinal problems

# Additional File

Additional file 1: Standard Protocol Items: Recommendations for Interventional Trials (CONSORT) 2010 Checklist: recommended items to address in a clinical trial protocol and related documents.

# Figures

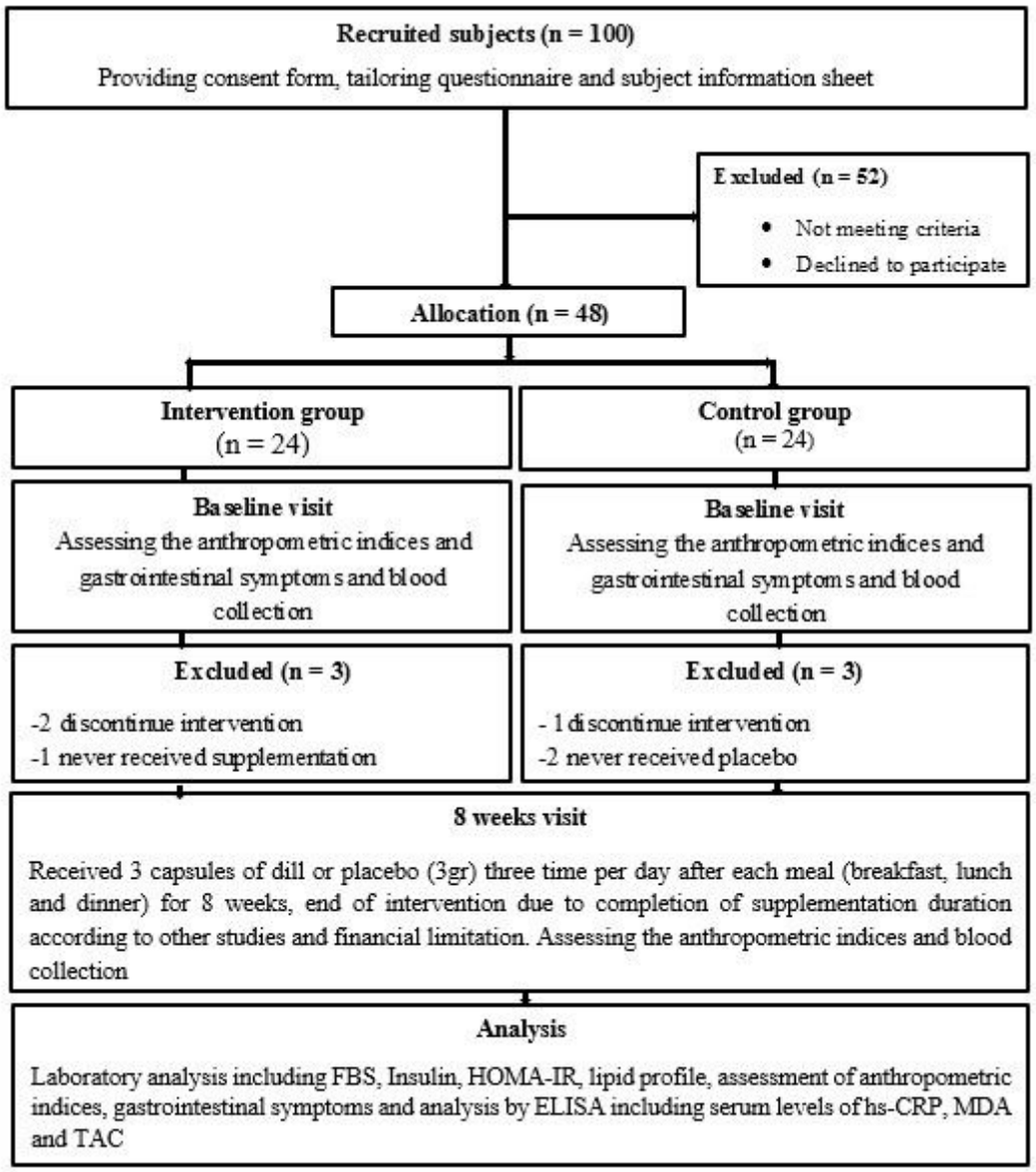


**Figure 1**

Stages of clinical trial progress

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf
- CONSORT2010Checklist.pdf