

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: a double-blind, placebo-controlled trial

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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 type 2 diabetic patients were randomly allocated to intervention and control groups and received either 3 gr dill powder or placebo (3 capsules 1 gr) three per day. 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 subjects at baseline and post-intervention. **Results:** The dill powder supplementation significantly decreased the mean serum levels of insulin, HOMA-IR, LDL-C and MDA in the intervention group in compare with baseline ($p < 0.05$). Also, the mean serum levels of HDL and TAC was significantly increased in the intervention group in compare with baseline ($p < 0.05$). Colonic motility disorders was the only gastrointestinal symptom that its frequency was significantly reduced by supplementation ($P = 0.01$). The mean changes of insulin, LDL-c and MDA were significantly lower in intervention group in compare with control group ($p < 0.05$). In addition, the mean changes of HDL was significantly higher in intervention group in compare with control group ($p < 0.05$). **Conclusion:** It is recommended that dill powder supplementation may be effective in control of the glycemic, lipid, stress oxidative and gastrointestinal symptoms in type 2 diabetic patients.

Introduction

Diabetes is a public health problem affecting 285 million adults, in 2010, and will increase to 7.7% and 439 million adults by 2030 (1). In Iran, it has been estimated that 8% of adult population have diabetes (2). Major characteristic features 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). Moreover, inflammatory cytokines contribute to T2DM occurrence by affecting beta cell function, and is in turn promote long-term complications of diabetes by intensifying hyperglycemia (5). Increased glucose uptake by endothelial cells in hyperglycemic conditions also leads to increased production of free radicals, which decrease levels of antioxidants (6). Besides, it is commonly reported that patients with T2DM are involved in gastrointestinal complications including gastro-esophageal reflux disease (GERD), gastroparesis, enteropathy, nonalcoholic fatty liver disease (NAFLD) and glycogenic hepatopathy (7).

Anethum Graveolens L, known as Dill, is a commonly used herb as a remedy and spices in foods (8). It is growing in the Mediterranean region, Europe, central, southern Asia and widely cultured in southeastern region of Iran (9). *Anethum Graveolens* (AG) leaves are a source of minerals, proteins and fibers (10). AG oils are also the potential source of antioxidant and also have antimicrobial and antispasmodic properties (11). In the traditional herbal medicine, AG is used for some 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, administration of different extractions of AG seed had antioxidant, hypolipidemic, and hypoglycemic effects (14). Earlier studies reported controversial findings for the protective effect of AG on lipid profile and insulin resistance in patients with metabolic syndrome (15, 16). Randomized clinical trials showed that AG reduced total cholesterol (5) and low density lipoprotein cholesterol (LDL-C), while did not change triglyceride and high density lipoprotein cholesterol (HDL-C) in patients with type 2 diabetes mellitus (T2DM) (17). It is also reported that AG could have beneficial effects on some inflammatory biomarkers (18), and controversial effects on glucose and insulin (18, 19). Besides inconclusive results considering glycemic, lipid and inflammatory profile, it is not clear whether AG help improve antioxidants and gastrointestinal symptoms. Therefore, the present study was designed to examine the effects of AG powder on 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

In this double-blinded (participants and investigator), placebo-controlled and single center trial 100 Type 2 diabetes patients were recruited from endocrinology and metabolism clinics of Golestan Hospital of Ahvaz Jundishapur University of Medical Science, Iran in 2017-2018 (Fig 1).

Inclusion criteria : Patients with DM (no more than five years since diagnosis); aged 30- 60 years; with gastrointestinal symptoms; body mass index (BMI) range between 25 to 35 kg/m²; without systemic diseases, thyroid disease, kidney disorder; not pregnant and lactating women; were not taking any dietary supplements or antioxidants, and immunosuppressant and anti-inflammatory agents. Exclusion criteria : Noticeable change in the dose of medications and treatment of diabetes, the ones were refusing to continue the participation in the study, and the subjects who had less than 90% compliance with dill capsules.

Diagnosis of DM was done based on the American Diabetes Association guidelines. Patients with FBS ≥ 126 mg/dl or 2-hour glucose) 2 hpp (≥ 200 mg/dl or HbA1c $\geq 6.5\%$ were diagnosed as diabetes mellitus (20).

Fifty two patients were excluded from study (because of 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. Multi-part questionnaire including demographic data (age and sex), anthropometric indices, dietary intake, medication, diabetes duration (in years), physical activity, gastrointestinal symptoms was obtained from 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 capsules remaining. Patients were excluded from study if had consumed less than 90 % of prescribed capsules. 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 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 intake

Dietary intakes were investigated with a 24-h food recall for 3 days (2 week days and 1 weekend day), and dietary intake was analyzed by software Nutritionist 4 specified for Iranian foods. Anthropometric 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 and short 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 hadn't gastrointestinal symptoms, 1: patient had occasional gastrointestinal symptoms, and $2 \leq$: 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 ($3000 \times g$, 10 min, $4^{\circ}C$). 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 (mombind). Insulin resistance was estimated according to the Homeostasis Model Assessment (HOMA) calculated as: $\text{HOMA-IR} = \text{fasting concentrations of glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL}) / 405$ (22). Friedewald formula was used for calculation of LDL (23):

$$\text{LDL-c (mg/dL)} = \text{TC (mg/dL)} - \text{HDL-c (mg/dL)} - \text{TG (mg/dL)}/5 \text{ (VLDL)}, \text{VLDL} = \text{TG (mg/dl)}/5$$

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).

Sample size calculation

The sample size (95% confidence interval and 80% power) was computed according to Mobasseri and coworkers' study (24) and considering LDL-C as the main outcome. Sample size was 21 subjects for each group. 24 subjects were computed in per group with withdraw 10%.

Outcomes

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

Statistical analysis

All statistical analysis was performed using SPSS 25. All data were reported as mean \pm standard deviations (SD) for quantitative variables or number (percentage) for qualitative variables. Normal distribution of data was checked using Kolmogorov-Smirnov test. Paired sample t-test was also used to compare the results within groups post-intervention. Independent sample t-test was done to compare the results between the two groups (placebo and intervention). Also, Independent T-test was used to identify differences between two groups at the end of study. Analysis of covariance (ANCOVA) was used to identify any differences between two groups at the end of study, adjusting for baseline values and covariates. Also, Chi square test was done 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, energy, macro and micro nutrient intakes

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 ($P \geq 0.05$) 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 seen 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 ($P \geq 0.05$) (**Table 2**).

Glycemic control

The results of this study showed that no significant differences were seen in FBS, insulin and HOMA-IR between 2 groups at baseline ($P \geq 0.05$). 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 $\mu\text{U/ml}$, 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 ($P = 0.012$) lower in the intervention group in compare with control group after the intervention (-2.7 ± 3.83 vs -0.81 ± 6.26 , 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 significantly ($P = 0.05$) lower in the intervention group in compare 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 compare with baseline (41.85 ± 11.68 to 44.80 ± 9.89 mg/dl, respectively; $P = 0.007$). Also, the mean changes of serum levels of HDL were significantly higher in the intervention group in compare with 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 level of LDL-C was significantly decreased post-intervention (81.00 ± 34.79 to 71.23 ± 26.63 mg/dl, respectively; $p = 0.029$). Furthermore, the mean changes of serum levels of LDL-C were significantly lower in the intervention group in compare with 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 between two groups ($P = 0.04$). However, no significant changes were seen in the mean serum levels of TG and TC after the intervention ($P \geq 0.05$) (**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 ($P \geq 0.05$). The results of present study showed that in intervention group the mean of MDA was reduced significantly post-intervention in

compare with baseline (3.34 ± 2.05 to 2.22 ± 1.57 μM , respectively; $P = 0.034$). At the end of study, there was significantly 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 compare 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 seen after the adjusting of confounding factors ($P = 0.004$). No significant difference was observed for hs-CRP within and between two groups ($P \geq 0.05$) (**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 compare with baseline ($P \geq 0.05$). Colonic motility disorders was the only gastrointestinal symptom that its frequency was significantly reduced by supplementation ($P = 0.01$), and this decrease had more happened in patients who had more severe gastrointestinal problems. However, in the control group, there was no significant reduction in the frequency of the gastrointestinal symptoms ($P \geq 0.05$).

Discussion

The present study revealed that 8 weeks of supplementation with 3 g/day AG had beneficial effects on reducing serum insulin and HOMA-IR. Moreover, AG could significantly reduce serum levels of LDL and enhance HDL compared with placebo. Patients in the intervention group had lower MDA and TAC; however, no significant change was observed for serum levels of hs-CRP. In terms of gastrointestinal symptoms, colonic motility disorders were only decreased.

The present findings are in line with those of several interventional studies confirming the benefits of AG in T2DM and metabolic syndrome (14, 25). The findings of significant reduction in HOMA-IR and serum levels of insulin which indicate that AG has a role 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 powder of Anethum for 8 weeks could significantly reduce levels of insulin (17). After 6 weeks of supplementation with 1.5 g/day 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 reduced levels of FBS in diabetic patients. High content of antioxidants (i.e. vitamin C, polyphenols, and carotenoids) in AG neutralize reactive oxygen species, and therefore, have a role in repairing of beta cells function and insulin secretion (26, 27).

In present study, serum concentrations of LDL decreased and HDL increased significantly at the end of the study. Whereas, no significant change was seen for serum levels of TG and TC. In agreement with our study, Rashidlamir et al. (28) showed that aerobic training with usage of 900 mg/day AG resulted in increased HDL and decreased LDL to HDL ratio in diabetic women compared with control group; however, findings from TG and TC was not statistically significant. In contrast, supplementation with 650 mg/d Anethum tablets twice daily increased serum levels of TG in patients with hyperlipidemia, but no significant changes were seen in TC and LDL (29). Treatment of hyperlipidemic patients with 1 g/day AG leave powder for 4 weeks duration resulted in a significant reduction in the levels of TC, TG, LDL and VLDL compared with patients treated with 20mg/day lovastatin tablets; however, no significant change was observed in serum levels of HDL. The exact mechanism of lipid-lowering effects of AG is not yet determined. But it may refer to decreased absorption of cholesterol by binding to bile acids, inhibition of cholesterol and fatty acid synthesis through suppression of acetyl-CoA carboxylase and HMG-CoA reductase activity, and stimulating cholesterol clearance by increasing LDL receptors (30-32).

In the current study, compared with patients in the control group, those received 3 g/day AG had lower levels of MDA and higher levels of TAC in both crude and adjusted models. MDA is a final product of lipid peroxidation recognized as an atherogenic agent. Patients with elevated levels of MDA are more susceptible to atherosclerosis, diabetes, and other metabolic disorders (33). Findings from animal studies showed that administration of different fractions of AG in animals fed with a high-fat diet decreased the MDA levels, and increased the activities of antioxidant enzymes including superoxide dismutase (SOD) and catalase. It is further increased the level of glutathione (GSH) playing a key role in scavenging ROS (34). Hamsters treated with AG extract or tablet exhibited a significant rise in TAC level compared with those under high cholesterol diet (35). AG is composed of various content of antioxidant such as flavonoids capable of scavenging free radicals (36). The enhanced levels of antioxidant activities in response to AG might be due to the content of polyphenols and flavonoids. Normal levels of antioxidant is supposed to protect individuals against several chronic diseases (37).

We observed non-significant decrease in serum levels of hs-CRP after supplementation with AG. The fact that an increase in the body weight is an indicator of inflammation (38) may be the reason of non-significant reduction observed in serum levels of hs-CRP in our study. Anti-inflammatory effects of different forms of AG have been shown in several animal studies (39-41). Payahoo et al. (18) found a significant decrease in serum levels of inflammatory biomarkers including hs-CRP, IL-6, and TNF- α after 8 weeks of supplementation with 3.3 gram dill powder.

In terms of gastrointestinal symptoms, we only observed a significant decrease in colonic motility disorders. It is reported that the most prevalent symptoms among diabetic patients are colonic motility disorders, which increase with age (42). Moreover, the prevalence of gastrointestinal symptoms is positively associated with duration of diabetes (42, 43). Patients included in the current study had a mean age of 50 years and a mean disease duration of 8 years which are relatively high, which could be a reason for the observed findings in this regard. Earlier animal models showed that AG extract is a potent

relaxant of contractions in rat ileum and have antisecretory and anti-ulcer activity against HCl- and ethanol-induced stomach lesions (44, 45).

To the best of our knowledge, this is the first human study investigating the effects of AG on gastrointestinal symptoms. The major strength of the present study was designing a well-controlled double-blind clinical trial, with controlling for several main confounding factors in different models. There are some limitations to our study. First, this is a single-dose trial preventing from any dose-effect association. It remains unclear whether higher doses could introduce a stronger clinical effect or vice versa. Second, the narrow range of inclusion criteria lead to unrepresentative samples that limit generalizability of the study results to all diabetic patients.

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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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

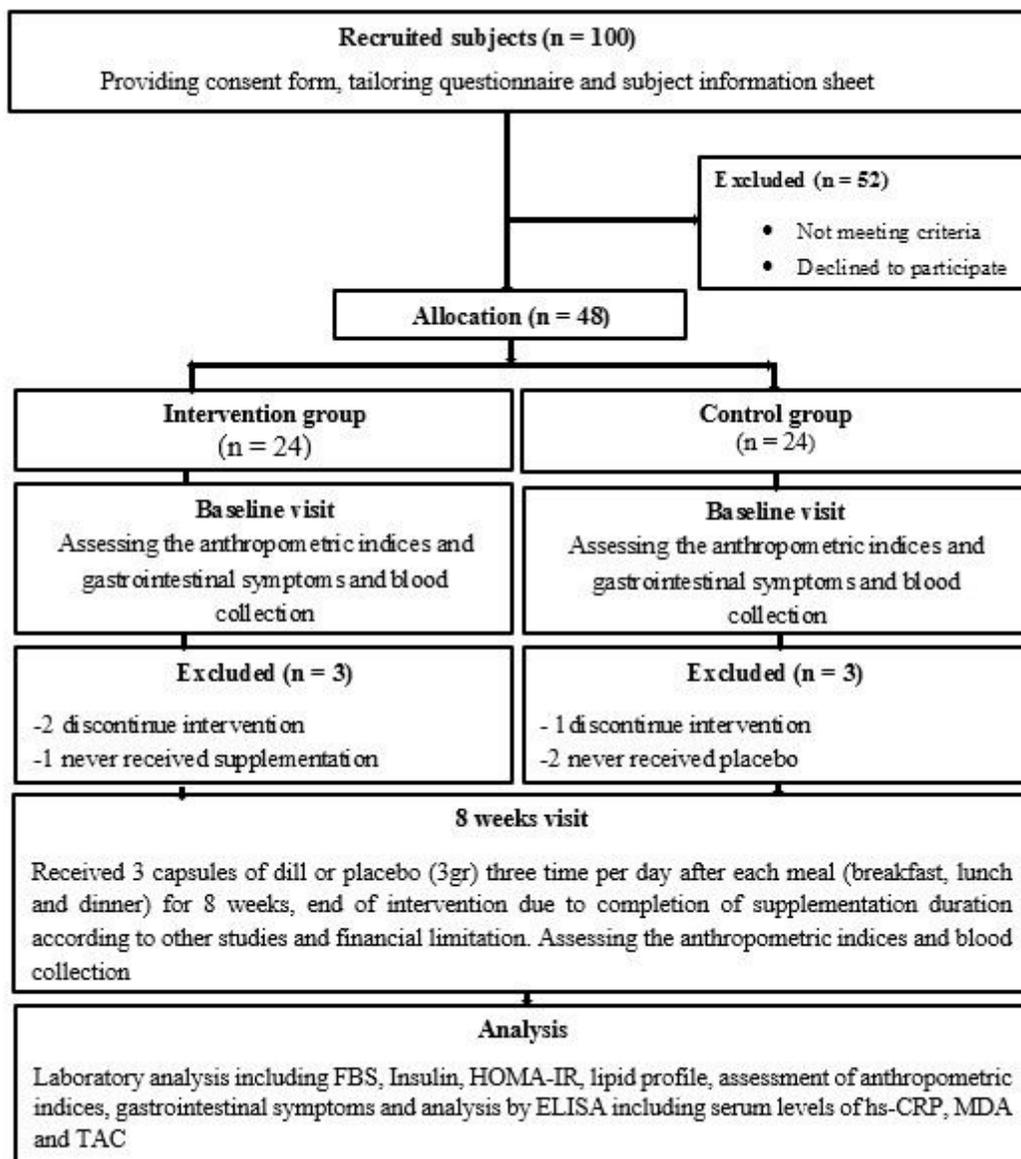


Figure 1

Stages of clinical trial progress

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