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Research paper

Changes of body composition and circulating adipokines in response to *Nigella sativa* oil with a calorie restricted diet in obese women

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ABSTRACT

Aim: Adipose tissue is an active endocrine organ with a key role in metabolic regulation and hormonal signaling. This study determined the effects of *Nigella sativa* (NS) oil with a low-calorie diet on body composition and adipokine levels in obese women.
Method: In this double-blind, placebo-controlled, randomized, clinical trial, 50 obese women were recruited. The participants were randomly divided into an NS oil group (n = 25) and a placebo group (n = 25), and each group received either a low-calorie diet with 3 g/day NS oil or a low-calorie diet with 3 g/day placebo for 8 weeks. Body composition and biochemical parameters were measured at the baseline and at the end of the trial.
Results: All 50 participants completed the trial. The participants reported no serious side effects, and the liver enzymes did not change significantly after the intervention. Mean BMI of the participants was $32.0 \pm 1.5\ kg/m^2$ at the baseline. NS oil decreased body fat mass (−9.5 vs. −2.9%; $p < 0.01$) and insulin levels (−29.3 vs. −8.6%; $p = 0.04$) and increased adiponectin levels (87.5 vs. 39.4%; $p = 0.03$) in the NS oil group compared to the placebo group after 8 weeks. At the end of the study, changes in BMI, insulin sensitivity, and the nuclear receptor PPAR-γ were not significant.
Conclusion: NS oil supplementation combined with a low-calorie diet can modulate hormone secretion and body composition in obese women. However, more studies are needed to clarify the efficacy of NS oil as an adjunct therapy for obesity management.

1. Introduction

Adipose tissue is a highly active endocrine organ which plays a key role in energy homeostasis, response to hormone signaling, metabolic regulation, and adipokine secretion. Adipose tissue secretes more than 50 signaling molecules and hormones called adipokines (Harwood, 2012). Adipokines are involved in the regulation of thermogenesis, appetite, glucose metabolism, insulin sensitivity, and other endocrine functions (Harwood, 2012; Gown et al., 2014). Adiponectin, a 30-kDa protein with anti-inflammatory and insulin-sensitizing actions, is an adipokine secreted exclusively from adipose tissue. It is involved in glucose and lipid metabolism and has an important role in decreasing insulin resistance and the risk of cardiovascular diseases (Fiaschi et al., 2014). Another important adipokine and a transcription factor abundantly expressed in adipose tissue is peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ has key roles in the regulation of fat generation, adipogenic differentiation, and insulin sensitivity (Ahmadian et al., 2013).

In obesity, the normal interaction between signals to and from adipocytes (a hormonal and metabolic feedback system) is disturbed by fat accumulation in the adipocytes. Insulin sensitivity and the secretion of adiponectin and PPAR-γ hormones decrease with obesity, and the risk of atherosclerosis and cardiovascular diseases increases (Torres-Fuentes et al., 2015). Previous studies have reported that adiponectin and PPAR-γ levels increased after losing weight through a calorie-restricted diet (Kotidis et al., 2006; Puglisi and Fernandez, 2008; Verreth et al., 2004). A calorie-restricted diet is the first-line therapy for losing weight. However, due to difficulties in adhering to a low-calorie diet for weight loss, obese subjects, particularly in Eastern societies often have a high tendency to take anti-obesity herbal supplements (Yun, 2010).

Abbreviation: ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BMI, body mass index; FBS, fasting blood sugar; FM, body fat mass; NS, *Nigella sativa*; PPAR-γ, peroxisome proliferator-activated receptor gamma; QUICKI, quantitative insulin sensitivity check index; RAS, random allocation software; TQ, thymoquinone.

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Some studies have indicated that the medicinal herb, *Nigella sativa* (NS) has anti-obesity properties (Datau et al., 2010; Le et al., 2004; Zaoui et al., 2002; Meddah et al., 2009).

The genus *Nigella* belongs to the buttercup or *Ranunculaceae* family. NS, also known as black cumin or black seed, is widely grown in Eastern Europe, the Middle East, and Western Asia. NS contains different active ingredients, including thymoquinone (TQ), thymol, nigellone, nigellicine, alpha-hederin, unsaturated fatty acids, vitamins (B1, B3, B6, E) and minerals (Fe, Zn, Cu) (Ali and Blunden, 2003; Heshmati and Namazi, 2015). In Iranian traditional medicine, NS has been used to promote health and treat several diseases, such as rheumatoid arthritis, dermatological diseases, digestive disorders, dyslipidemia, and diarrhea (Heshmati and Namazi, 2015; Namazi et al., 2015a). Studies have shown the antimicrobial, immune-stimulatory, anti-inflammatory, antioxidant, anti-diabetic and anti-obesity effects of NS in animal models and clinical trials with no reports of toxicity or serious side effects (Meddah et al., 2009; Heshmati and Namazi, 2015; Ali and Blunden, 2003).

Limited studies have evaluated the effects of NS on obesity and insulin sensitivity with conflicting results (Qidwai et al., 2009; Najmi et al., 2008; Heshmati et al., 2015). To the best of the author's knowledge, the present study is the first to evaluate the effects of NS oil combined with calorie restriction on fat-derived hormones in obese subjects. Therefore, the aim of this study was to determine whether NS oil combined with a low-calorie diet could improve body composition and adipokine levels in obese women.

2. Materials and methods

2.1. Participants

Trial subjects consisted of 50 obese females who had visited Sheykhoraees Clinic in Tabriz, Iran between April to July 2014. Inclusion criteria included gender (female), age (between 25 and 50 years), and body mass index (between 30 kg/m^2 and 35 kg/m^2), while excluded were individuals with a history of cardiovascular, renal, hepatic, diabetes mellitus or pancreatic disorders; a history of smoking; adherence to a weight loss diet or the use of anti-obesity drugs over the past 6 months; consumption of aspirin, vitamin K, or any other anticoagulant drugs; pregnancy and lactation; or the consumption of any herbal medicines, antioxidants or anti-inflammatory medications. General characteristics collected through participant interviews included age, family history of obesity, consumption of medicine, and medical history.

2.2. Study design and randomization

Subjects of the present clinical trial, which involved a randomized double-blind placebo-controlled design, were randomly allocated through a block randomization procedure into two groups based on their body mass index (BMI) and age. Each arm of the trial included two cases in every permuted block, and all case allocations were conducted randomly by RAS (Random Allocation Software). Based on previous research (Datau et al., 2010) and considering body weight changes, sample size was determined. The minimum resulting sample size was calculated at 20 subjects, resulting in a 95% confidence level and 80% power for each treatment group. The sample size was ultimately raised to 25 people to compensate for a 25% dropout rate. The trial was conducted according to the guidelines established in the Declaration of Helsinki, and approved by the Ethics Committee of Tabriz University of Medical Sciences, and informed written consent was obtained from the participants. The trial was registered on the Iranian registry of clinical trials (www.irct.ir/, IRCT201106191197N10).

2.3. Intervention

All the participants received a moderate fat, nutrient-balanced reduction diet. A dietician designed an individual diet by using the Mifflin equation to determine resting energy expenditure (Namazi et al., 2015b). After adding the estimated physical activity coefficient (based on International physical activity questionnaire) and thermic effect of food coefficient (1.1), 500 kcal from the amount of total required daily energy calculated for each subject was subtracted. The resulting diet was composed of 15% protein, 55% carbohydrates, and 30% fat. A 24-hour dietary recall (one weekend day and two weekdays) was applied for assessing the level of patients' compliance with the diet.

NS oil soft gel capsules were administered to the treatment group for 8 weeks at a dose of 3 g/day, with patients ingesting one capsule (1 g NS oil) 30 min before each main meal (breakfast, lunch and dinner), and the same dosage of sunflower oil (SF) was given to the placebo group. Similar opaque bottles were used to present both capsules of NS oil and SF oil to participants. Half of the bottles were distributed among subjects at the beginning of the trial, and the remaining bottles were distributed in the middle of the trial. After randomization, volunteers received supplements in compliance with allocation codes. In order to maintain 'blinding', this procedure was carried out by an investigator who had no clinical involvement in the study. In addition to participants, clinical and laboratory staff were kept 'blind' until the end of data analyses to ensure reliable randomization and allocation. Contact with subjects was maintained through a weekly phone call in an effort to minimize dropouts and to make sure that participants were ingesting assigned supplements. Volunteers were asked to inform research staff immediately in the event of any suspicious reactions to supplements. Participants were also asked not to change physical activities and to inform researchers if they consumed any drugs or changed their physical activities during the experimental period. Upon returning their bottles to researchers after the trial, participants' compliance with the plan was determined by counting remaining capsules in each bottle. Patients who had consumed fewer than 95% of the supplements in each visit were excluded from the trial.

2.4. Characteristics of supplements

Soft gel capsules of NS oil and SF oil, similar in color and size, were prepared by Daana Pharmaceutical Company. (Tabriz, Iran). A cold press procedure with a yield of 30% was used to prepare the NS oil, and measurements of fatty acid content of both oil supplements were presented in our earlier study (Mahdavi et al., 2015). Sunflower oil was chosen as a placebo based on previous studies (Gonzales and Gonzales, 2014; Ballard et al., 2002). Participants and researchers were not aware of treatment details, and bottles containing capsules were coded as A or B by an individual who was not involved in the trial.

2.5. Measurements

The primary outcomes of the present study based on the aims of study were the effects of NS oil supplementation with a low-calorie diet on BMI, serum levels of insulin, adiponectin, peroxisome proliferator-activated receptor **γ** (PPAR-γ) and insulin sensitivity in obese women. The secondary outcome was the effects of NS oil supplementation with a low-calorie diet on liver enzymes in obese women. At baseline, and at the end of the study, anthropometric indices, physical activity, dietary intake and biochemical parameters were evaluated. Measurement of anthropometric indices, physical activity and dietary intake were described elsewhere (Mahdavi et al., 2015).