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ORIGINAL PAPER

Clinical Evaluation of *Nigella Sativa* Seeds for the Treatment of Hyperlipidemia: a Randomized, Placebo Controlled Clinical Trial

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Background: Natural products are proved to play a good role as an alternative to synthetic chemicals in many clinical conditions. Hypercholesterolemia is the most important risk factor for atherosclerosis. Previous studies showed that *Nigella sativa L.* has both antioxidant and lipid lowering potentials. **The aim of this study** was to evaluate the efficacy of the seeds of *Nigella sativa* on the treatment of hyperlipidemia. **Methods:** In this randomized, placebo controlled clinical trial which was conducted in Isfahan city (Iran), 88 subjects aged ≥ 18 years with a total cholesterol concentration > 200 mg/dl were included. According to the patients` profiles number, they were randomized to receive either *N. sativa* capsules or the matching placebo. Each *N. sativa* capsule contained 500 ± 10 mg *N. sativa* crushed seeds, and patients had to take 2 g *N. sativa* per day for 4 weeks. Fasting baseline laboratory values (Fasting blood sugar, Total cholesterol, Low density lipoprotein, High density lipoprotein and Triglyceride) were obtained for all parameters on each subject prior to the start of the study and at the end of 4 weeks. **Results:** In our study a significant decrease was observed in the concentration of total cholesterol (4.78%), Low density lipoprotein (7.6%) and Triglyceride (16.65%), and this decrease was more significant for TG concentration. *N. sativa* had not any beneficial effects on Fasting blood sugar and High density lipoprotein. **Conclusion:** According to the results of our present study it seems that *N. sativa* may have some beneficial therapeutic effects in the treatment of hyperlipidemia. However, further investigations with a larger sample size are necessary. **Key words: *Nigella sativa*, Hyperlipidemia, Clinical Trial, Ethnopharmacology.**

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1. INTRODUCTION

Atherosclerosis is the major cause of death and disability (1). It causes death almost two times more than cancer and 10 times more than the deaths caused by accidents (2). Atherosclerosis is a multifactorial disorder. And hypercholesterolemia is its major risk factor. It is shown elsewhere that, 1% reduction in serum cholesterol reduces the risk for CHD by 2% (2). A rise in total cholesterol (TC) in men from 200 to 240 mg is considered to be linked to a three-fold increase in death from cardiac disease (3).

Some natural products have been considered to play a good role as an alternative to synthetic chemicals in this clinical condition. A wide variety of plants has been reported to have lipid lowering activity (4). Among such plants *Nigella sativa L.* (Black seed) in several studies has been investigated for its lipid lowering effects on animals (5, 6, 7). Other than the safety matter, researchers have showed many beneficial pharmacologic actions for this plant, including hypotensive (8), antitumor (9), hypoglycemic (10), anti inflammatory (11), anti asthma (12), antiallergic (13), and antioxidant properties (14). Some other pharmacological effects like anti microbial (15), anorexic (6), lactagogue and diuretic roles were also reported (16). It is also famous for the saying of the great Prophet Mohammad (peace be upon him) "in the black seed there is healing for every illness except death". it can also be used as a natural food and additive (9).

Several studies have showed lipid lowering effect of *N.sativa* in animal models (5, 6, 7). *N. sativa* is a rich source of polyunsaturated fatty acids like linoleic (55.6%) and oleic acid (23.4%), it also contains minor amount of linolenic, arachidonic, and eicosenoic acids. Unsaturated fatty acids constitute 80-

84%, and saturated fatty acids constitute 14-20% of fatty acids in black seed (17). Its essential oil contains antioxidant components such as thymoquinone and para-cymene, which act as a free radical scavenger (14). Some alkaloids like nigellimine, nigellidine, and nigellicine can be found in the seeds (18). It also contains fat-soluble vitamins, potassium, calcium, phosphorus and iron (14).

Some small and short-term studies have been carried out previously to evaluate hypolipidemic effect of *N. sativa* on humans (9, 16). The aim of this study was to investigate the probable lipid lowering effects of the seeds of *N. sativa* with a more reliable methodology and a larger sample size in hyperlipidemic adults.

2. PATIENTS AND METHODS

In this a randomized, placebo-controlled clinical trial, which was conducted in the Cardiovascular Research Institute, affiliated to the Isfahan University of Medical Sciences Isfahan (Iran), from July 2010 until June 2011; 88 patients were recruited from the outpatient clinics. The main criterion for entry of adult aged ≥18 years was a total cholesterol concentration more than 200 mg/dl. Subjects taking lipid-altering medication within 6 weeks prior to the study were excluded. Other exclusion criteria were pregnancy, lactation, current smoking, having diabetes mellitus, cardiovascular disease, renal or liver disease, thyroid dysfunction, or other lipid altering disease. According to the patients' profiles number and the random figures tables, they were randomized to receive either *N. sativa* capsules or the matching placebo. Both types of capsules were identical in appearance. Each black seed capsule contained 500 $\pm$ 10 mg *N. sativa* crushed seeds, and patients had to take 2 g of *N. sativa* per day for 4 weeks. They were instructed to take 2 capsules before breakfast and 2 capsule in the afternoon prior their food. Subjects were also asked not to change their usual daily diet and physical activity during the study. Fasting baseline laboratory values (including fasting blood sugar and lipid profile indice) were obtained for each subject prior to the start of the study and at the end of the 4 weeks. Subjects were asked to record adverse effects and the number of capsules they consume, in order to control their cooperation. Lipids and lipoproteins were analyzed using standard enzyme-based biochemical analysis.

N. sativa seeds were obtained from a small farm in Hounejan in Isfahan Province (Iran) at an altitude of approximately 1,650 meter in September 2009. The plant was recognized and authenticated by a registered botanist in the Herbarium Department of Tehran Islamic Azad University, Tehran, Iran. Voucher specimen has been preserved for reference (HN-1100) in the Herbarium of the Isfahan school of Pharmacy

All patients have completed informed consent forms, and the study protocol was approved by the board ethics for human research at Isfahan University of Medical Sciences.

All data were analyzed using SPSS® for windows (v. 18). We have used Mann-Whitney U test and Wilcoxon Signed Ranked test for quantitative data and chi-squared test for qualitative data, considering p<0.05 as significant.

Variable	Cases (n=37)	Controls (n=37)	P value
Gender (% male)	54.1	56.8	0.355*
Age (years)	40.38	38.4	0.575**
BMI§ (cm/kg2)	25.01	23.19	0.140**

* Chi-squared test, **Man Whitney U test , §Body Mass Index

Table 1. Baseline characteristics of subjects in the case and control groups

	Cases (n=37)			Controls (n=37)		
	Before Mean±SD	After Mean±SD	P value*	Before Mean±SD	After Mean±SD	P value*
Total cholesterol (mg/dl)	235.24±28.29	224.00±32.39	<0.001	233.39±26.24	231.31±25.73	0,295
Triglyceride (mg/dl)	173.91±69.35	144.94±68.30	<0.001	173.88±47.92	181.16±43.96	0,116
High-density lipoprotein (mg/dl)	51.48±15.45	52.76±14.33	0,166	48.03±8.70	47.65±7.15	0,716
Low-density lipoprotein (mg/dl)	144.58±19.06	133.51±21.78	<0.001	138.36±19.05	135.81±20.37	0,163
Fasting blood sugar (mg/dl)	86.62±11.95	86.12±11.66	0,422	83.58±9.70	85.35±9.70	0,276

*Wilcoxon Signed Ranked Test

Table 2. The lipid profile of cases and controls after a 4-week usage of black seed capsule formulation.

3. RESULTS

Number of 14 subjects were excluded during the study, because of altering their usual diet and being irregular in taking capsules, so we did our statistical analysis on 74 patients (37 subjects in black seed group and 37 subjects in placebo group) who fully completed the study. All patients were statistically matched in terms of age, gender, and body mass index (BMI) (Table 1). No complication or adverse effect was reported by subjects. Changes of lipid profiles after 4 weeks of therapy are shown in Table 2. Triglyceride (TG) and Fasting blood sugar (FBS) increased and total cholesterol, LDL-cholesterol and, HDL-cholesterol were reduced in placebo group (controls). These changes were not statistically significant. (P value > 0.05).

In the treatment group (cases), the mean values at the baseline for total cholesterol were, 235.24 mg/dl; for LDL, 144.58 mg/dl; for HDL, 51.48 mg/dl; for TG, 173.91 mg/dl, and for FBS it was 86.62. After two months, these values for cholesterol, LDL, HDL, TG, and FBS were, 224.00mg/dl, 133.51 mg/dl, 52.76 mg/dl, 144.94 mg/dl, and 86.12 mg/dl respectively.

In the treatment group LDL cholesterol and total cholesterol levels were decreased by 7.6% and 4.78%, respectively, and TG level was significantly reduced by 16.65%. Black seed had not any beneficial effects on FBS and HDL, no meaningful changes were observed in the mean FBS and HDL cholesterol, after 4 weeks, in black seed group.

4. DISCUSSION

Atherosclerosis is a multifactorial disease, and hypercholesterolaemia when due to an increase in LDL, is the

principal aetiological cause of it (19). The increased permeability of the endothelium in the presence of elevated concentration of LDL promotes accumulation of LDL particles in the intima. These particles undergo oxidative modification, which may lead to inflammatory reactions and initiate atherosclerosis process. So lowering LDL concentration and improving antioxidant defense of the body are two important ways to prevent atherovascular disease (6, 20).

N. sativa is a rich source of polyunsaturated fatty acids. Its fatty acid composition satisfies the WHO standards. This standard claims that dietary fat should be rich in polyunsaturated fatty acids (more than 33%) and with decreased components of saturated fatty acid (less than 33%) (6, 17).

The cholesterol lowering effect of *N. sativa* may be attributed to the presence of phytosterols like Beta-sitosterol, polyunsaturated fatty acids and its antioxidant activity. *N. sativa* may be able to reduce synthesis of cholesterol by hepatocytes and lower its absorption from the small intestine (21); It may also activate LDL-receptor by decreasing intracellular cholesterol, witch leads to rapid clearance of LDL-cholesterol from blood circulation (9). The effect of *N. sativa* on increasing cholesterol secretion in the bile is another probable mechanisms witch can enhance its cholesterol lowering properties (16). Morikawa et al. has shown that nigellamine has a potential for lowering Triglyceride levels in primary cultured mouse hepatocytes and this activity was equivalent to clofibrate (22). Additionally, its antioxidant components can inhibit lipid peroxidations, which is a key factor in the atherosclerotic process (14).

We used the whole seed rather than oil, because there may be some other effective components existing in the seeds that are not soluble in the oil (16).

According to Table 1, no statistically significant difference was observed between the patients' demographic characteristics in the intervention and control group of patients in terms of age, gender and BMI (P value > 0.05).

According to Table 2, a statistically significant reduction was observed in the serum concentration of the total cholesterol, LDL cholesterol and TG (P value < 0.001). Since we asked all subjects not to change their usual daily diet, it seems that this decrease maybe due to the result of consuming black seeds. N. sativa had no beneficial effects on FBS and HDL, in our research (P value: 0.422 and 0.166, respectively).

Bamosa et al. worked on effects of daily oral ingestion of 2 g *N. sativa* on some blood parameters for 2 weeks and reported a pattern of decreased levels of FBS and cholesterol on 16 second year medical students. There was no significant decrease in triglyceride level (9). Ibraheim et al. studied the effect of daily oral ingestion of 2 g *N. sativa* seeds on some blood parameters for 2 weeks on 18 female volunteers. In this research the levels of TC and LDL decreased while TG levels increased significantly (16). A significant lipid lowering effect of *N. sativa* in patients with metabolic syndrome as an add-on therapy was observed by Najmi et al. In their research, the treatment group (n=30) showed significant improvement with reference to total cholesterol and LDL (23).

Results of the present study are consistent with other previous studies, but lowering effect of *N. sativa* on TG was more significant in our study. Since black seed has both effect of antioxidant and hypercholesterolemic it maybe a useful medicine for hypercholesterolemia. On the other hand, researchers have shown that black seed is effective against hypertension and diabetes, which are two important risk factors for atherosclerosis. Toxicological studies for black seed on rat, has shown a wide margin of safety for therapeutic dose (7). Its safety, lack of side effects, and its rich nutritional profile are among the main reasons which make *N. sativa* a valuable herb.

It is important to mention that the period of our study was a short one and it is not clear for us whether the lipid lowering effect will persist with its long term of usage. Also, self-reported data for exercise and diet information may not be as precise as expected. Therefore, it is probable that the changes in diet or exercise may have affected on results.

5. CONCLUSION

According to the results of our study it seems that *N. sativa* may have some beneficial therapeutic effects in the treatment of hyperlipidemia. However, further multicentral and multi-national investigations with a larger sample size are still needed.

Conflict of interest: none declared.

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