

Effect of *Nigella sativa* supplementation on human lipids: systematic review

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ARTICLE INFO

Article history:

Received on: 07/01/2017

Accepted on: 13/03/2017

Available online: 30/04/2017

Key words:

Nigella sativa, black seeds, hyperlipidemia, human lipids, lipid profile.

ABSTRACT

Nigella sativa (NS) is widely used in traditional medicine and several studies have been conducted to reveal NS effects on different medical disorders including hyperlipidemia. Since hyperlipidemia is a common risk factor for the development of cardiovascular illness. We evaluated the effects of NS supplementation on lipid profile in clinical trial performed among humans. A search on published studies was done by using databases including Scopus, PubMed, Google Scholar, Thomas Reuters Web of Science, and CINAHL. Terms searched included “*Nigella sativa*, Black seed, Black cumin, Triglycerides, Cholesterol, Lipoproteins”. Initially 432 articles were extracted. However, four hundred eighteen papers were unrelated, reviews, animal studies, combined and duplicated studies were excluded, and finally only fourteen articles were eligible for this review. After analysing 14 articles including 738 participants from different countries and nations. Results of these clinical trials revealed that *Nigella sativa* is effective to change the lipid profile significantly in different conditions. This systematic review revealed that *Nigella sativa* supplementation might be effective in hyperlipidemic control in humans and seems potential target of future drug for hyperlipidemic conditions.

INTRODUCTION

Hyperlipidemia is a common risk factor for the development of cardiovascular illness (Graham *et al.*, 2007). Increased serum total cholesterol concentrations are directly associated with an increased risk for coronary heart disease (Navar-Boggan *et al.*, 2015). Pharmacologic treatment used for treating high-risk persons with lipid-lowering drugs include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), bile acid sequestrants, fibrates, and nicotines (Last AR *et al.*, 2011). None of the above pharmacologic options are free of adverse effects (Maron *et al.* 2000), and some have been associated with potential carcinogenicity (Newman and Hulley,

1996). Effective treatment with a harmless for lowering cholesterol levels would therefore be of considerable interest. For the past decade non-pharmacologic treatment has been by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program has recommended as initial therapy in most patients with hyperlipidemia (Expert Panel, 2011). *Nigella sativa* among the best rated evidence based herbal medicines (Ahmad *et al.*, 2013). *Nigella sativa* (NS) (Family Ranunculaceae) is a widely used medicinal plant around the world. It is very popular in various traditional systems of medicine like Unani, Ayurveda, Siddha and Chinese.

Seeds and oil have a long history of folklore usage in various systems of medicines and food. The seeds of NS have been widely used in the treatment of different diseases and illnesses. In Islamic literature, it is considered as one of the greatest forms of healing medicine. It has been recommended for using on regular basis in Tibb-e-Nabwi (Prophetic Medicine).

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It has been widely used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, anti-bacterial and in skin disorders. Extensive studies on NS have been carried out by various groups of researcher and a wide spectrum of its pharmacological actions have been explored which may include antidiabetic, anticancer, immunomodulator (Hmza *et al.*, 2013), analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties (Ahmad *et al.*, 2013). The seeds of NS are widely used in the treatment of numerous diseases like bronchitis, asthma, diarrhea, rheumatism and skin disorders. It is also has been reported that used as liver tonic, digestive, antidiarrheal, appetite stimulant, emmenagogue, to increase milk production in nursing mothers to fight parasitic infections, and to support immune system (Goreja, 2003; Khaled, 2009; Assayed, 2010; Boskabady *et al.*, 2010; Abdel-Zaher *et al.*, 2011; Abdel-Salam, 2012). Most of the therapeutic properties of this plant are due to the presence of thymoquinone (TQ) which is a major active chemical component of the essential oil. Black seeds are also used in food like flavoring additive in the breads and pickles because it has very low level of toxicity (Al-Ali *et al.*, 2008). There are a few review articles that have surveyed the effect of *N. sativa* on some diseases. However, we are going to conduct a systematic review of the literatures to identify relevant studies about the effect of *N. sativa* supplementation on human lipids.

METHODOLOGY

The protocol that was used in this study is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. A search of published studies was performed by using computer databases including Scopus, PubMed, Google Scholar, Thomas Reuters Web of Science, and CINAHL.

Literature Review:

A systematic review of the literature was conducted to identify relevant studies about *Nigella sativa* and human lipids/cholesterol. To conduct a comprehensive search of health science journals, we used Medline via Ovid Medline (published between 1946 and March 2015) and CINAHL via Ebscohost (published between 1946 and 2015). The search strategy involved a combination of the following two sets of key words; (1) *Nigella sativa* OR black seeds OR Habutulsuda, Black cumin OR thymoquinone; (2) Lipids OR cholesterol OR triglyceride OR hyperlipidemia.

Inclusion criteria

1. The effect of *Nigella sativa* on human lipids changes.
2. Clinical trial.

Exclusion criteria

1. Animal studies.
2. Review studies.

3. The effect of *Nigella sativa* on unrelated blood or clinical parameters.
4. The effect of *Nigella sativa* in combination with other plants or exercise.
5. Duplicated studies.

Selection of Research Articles

The results were limited to studies that were published in English language that included abstracts. To be included, studies had to (1) report the association or effect of *Nigella sativa* and human lipid changes. Papers were excluded if the studies were related to reviews, news, letter, editorials, or case studies.

Data Extraction and Management

We selected papers to be included in the review in three phases. First, we excluded any paper that did not match the inclusion criteria based solely on the title. Second, we screened all the abstracts of the remaining papers and then excluded a second group of papers that did not meet our inclusion criteria. Lastly, we read the remaining papers from the second phase to exclude any paper that did not meet our inclusion criteria. After the initial screening of the titles and abstracts, duplicates were removed and the remaining papers were again screened by at least two reviewers. The inclusion of the full papers into the review had to be agreed by at least two reviewers before the data extraction phase. Any discrepancies were resolved through discussion between the reviewers. Initially, 432 articles were extracted. After reviewing their titles and abstracts and removing unrelated, animal, and review studies, 312 articles (Medline; 206, Scopus; 90, EBSCO; 16) were retrieved for further evaluation. After excluding the animal studies, reviews, removal of abstracts due to duplicates and unrelated studies. Finally, 14 studies were considered eligible for our review [Table 1].

Table 1: Process of study selection.

Process	Selected studies
Initial search	432 papers
After exclusion of studies that were unrelated to this study.	312 papers
After exclusion of animal studies	67 papers
After exclusion of review studies	21 papers
After exclusion of combined studies	18 papers
After exclusion of duplicated studies (eligible for our review).	14 papers

RESULTS

Data extraction was performed independently from 14 studies and in a standardized manner with the use of a data collection form. We recorded the following data from the studies: (1) the type of study, (2) a brief description of the sample/population of the study; (3) a brief description of the methods used in the study; (4) the brief description of the results of the study; (5) comments and conclusion of the study (6) complications if any.

Table 2: Characteristics of human studies that eligible to the study.

Study/country	Type of study	Sample/population	Methodology	Results	Comments or outcomes	complications
1. Heshmati <i>et al.</i> 2015/ Iran	double-blind placebo-controlled randomized clinical trial	T2DM (n = 72)	Randomly divided into two groups using a block randomization procedure, based on sex, age and duration of diabetes. In every permuted block of patients, two subjects were allocated to each arm of the trial.	TC (-9.8%), TG (-4.3%), HDL-C (19%) and LDL-C (-17.6%) changed significantly in the intervention group compared to baseline.	NS oil can improve glycemic status and lipid profile in patients with T2DM.	No complications caused by NS were observed.
2. Ibrahim <i>et al.</i> 2014/ Malaysia	Experimental study (CT)	37 Women (45-69 year, menopause)	18 respondents were assigned to NS, 17 respondents placebo group, the case group were received NS for 2 months	Significant decrease in the development of hyperlipidemia among menopausal women in NS treatment group compared to placebo group.	NS has beneficial effects on lipid profile in menopause women.	No complications caused by NS were observed.
3. Qibi <i>et al.</i> 2006 /Iraq	Experimental study	10 Healthy population	Ten healthy volunteer age ranged 20-49 years. Non-smoker- non hypertensive patients, non DM, no CVD, no other medication that can influence lipid metabolism. 750 mg twice a day for 28 days.	↓TG, ↓LDL, ↓TC, ↑HDL	NS is a favorable effect on lipid profile of healthy individuals	No complications caused by NS were observed.
4. Najmi <i>et al.</i> 2012/India	Experimental study	80 Patients of metabolic syndrome/ 52 males and 38 females. Age 20 to 70	Group 1 (n=40) were advised to take metformin 500mg twice a day, atorvastatin 10 mg once a day Aspirin 150 mg for a period of 8 weeks; Group 2 (above medication)+500mg capsule of NS	↓TG , ↓LDL, ↓TC, ↑HDL	NS can be used as add on drug therapy in metabolic syndrome patients.	No complications caused by NS were observed.
5. Tasawar <i>et al.</i> 2011/Pakistan	Experimental study	80 patients with stable coronary artery disease	1)The interventional group given <i>Nigella sativa</i> seeds powder 500mg/daily and statin (10-20 mg) for 108 days. 2)noninterventional group given statin (10-20mg/daily) daily only .	↓TG , ↓LDL, ↓TC, ↑HDL, ↓VLDL	<i>Nigella sativa</i> is effective to change the lipid profile significantly	No complications caused by NS were observed.
6. Kaatabi <i>et al.</i> 2012/ KSA	Open-label, second phase trial study	94 DM patients (43 males and 51 females) with type 2,	94 patients were divided into 3 groups through simple random sampling and were administrated 3 different oral doses of NS (1g, 2g, 3g per day for 12 weeks)	Patients ingested 2g/day NS significantly decline in TC, TG, and LDL, and a significant elevation in HDL.	NS supplementation at a dose of 2g/day for 12 weeks may improve the dyslipidemia associated with type 2 DM.	No complications caused by NS were observed.
7. Najmi <i>et al.</i> 2008/India	Experimental study	60 patients with metabolic syndrome	60 patients divided into 2 groups of 30 each. 1)30 pts were advised to take (atorvastatin 10 mg once a day and metformine 500mg twice a day for a period of six weeks. 2)30 pts were advised to take (atorvastatin 10 mg once a day and metformine 500mg twice a day for a period of six weeks and N. Sativa 2.5 ml (oil)twice daily.	The treatment group showed significant improvement with reference to total cholesterol, low density lipoprotein, (LDL-C)	NS oil has a significant activity in dyslipidemic patients.	No complications caused by NS were observed.
8. Bhatti and Rehman, 2009/ Pakistan	Experimental study	10 pts Hypercholesterolemic patients ;	1g of SN powder before breakfast was orally administered for 2 months.	↓TG, ↓LDL, ↓TC, ↑HDL	The NS modify the plasma lipid profile in Hypercholesterolemic patients	No complications caused by NS were observed.
9. Sabzghabae <i>et al.</i> 2012/Iran	Randomized, placebo controlled clinical trial	88 subjects aged > or =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.	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 may have some beneficial therapeutic effects in the treatment of hyperlipidemia.	No complications caused by NS were observed.

10.	(Datau <i>et al.</i> 2010)/Indonesia	Experiment al, double blinded with placebo control, pre-test and post-test design	39 Subjects are 30-45 years old, divided into the treatment and control groups, and evaluated weekly for 3 months.		<i>Nigella sativa</i> could inhibit the decreasing of serum free testosterone. No side effects were detected in the treatment group.	It is suggested that larger dose and longer duration of NS consumption will give better results.	No complications caused by NS were observed.
11.	(Qidwai <i>et al.</i> 2009)/Pakistan	Randomized, double-blind trial.	123 subjects, Baseline and after-intervention variables recorded	Baseline and after-intervention variables recorded were the following: body-mass index, waist-hip ratio, blood pressure, fasting blood sugar, serum lipids, serum alanine aminotransferase, and serum creatinine.	Favorable impact of powdered <i>N. sativa</i> (Kalonji) seed in capsule was noted on almost all variables, but results were not statistically significant because of small sample size.	Favorable impact of powdered <i>N. sativa</i> (Kalonji) seed in capsule was noted on almost all variables,	No complications caused by NS were observed.
12.	Dehkordi, Kamkhah 2008/ Iran	randomized, double-blind, placebo-controlled trial	48 subjects	NS extract caused a significant decline in the level of total and low-density-lipoprotein (LDL)-cholesterol relative to baseline data.	NS extract caused a significant decline in the level of total and low-density-lipoprotein (LDL)-cholesterol relative to baseline data. No complications caused by NS were observed.		No complications caused by NS were observed.
13.	Bamosa <i>et al.</i> 1997/KSA	Clinical trial	12 health and 7 controls	2 capsules of 500mg <i>N.Sativa</i> twice daily. All parameters were tested after 2 weeks	Significant decrease of glucose, cholesterol	<i>N.sativa</i> has a potential reducing effect on the blood levels of both glucose and cholesterol	No complications caused by NS were observed.
14.	Ahmed <i>et al.</i> 2012)/Egypt	Experimental study	66 subjects/D M patients	The first group included 41 patients with T2DM. DM was diagnosed according to the ADA, 2012. The patients were chosen to be free of diabetic complications.	All subjects received oral <i>N. sativa</i> tea (5gm/day) daily for 6 months. This was added to their oral antidiabetic drugs in the patients group.	<i>N. sativa</i> tea improved the glycemic control and the lipid profile and increased PON-1 activity in T2DM.	No complications caused by NS were observed.

All studies were clinical trials and have been conducted on different patients and subjects (Heshmati *et al.*, 2015; Ibrahim *et al.*, 2014; Qibi *et al.*, 2006; Najmi *et al.*, 2012; Tasawar *et al.*, 2011; Kaatabi *et al.*, 2012; Najmi *et al.*, 2008; Bhatii *et al.*, 2009; Sabzghabae *et al.*, 2012; Datau *et al.*, 2010; Qidwai *et al.*, 2009; Dehkordi *et al.*, 2008; Bamosa *et al.*, 1997; Ahmed *et al.*, 2012). Information of these studies is summarized in the table 2.

The total number of subjects in these trials was 738 from different conditions and diseases as hyperlipidemia in diabetic patients (Heshmati *et al.*, 2015; Kaatabi *et al.*, 2012; Ahmed *et al.*, 2012), menopausal women (Ibrahim *et al.*, 2014), metabolic syndrome (Najmi *et al.*, 2012; Najmi *et al.*, 2008) and coronary heart disease (Tasawar *et al.*, 2011). The duration of the trials was between 2 weeks- 3 months. The dose of *NS* supplements was between 500 mg and 2 g per day and was administered orally in all studies. The age range of the participants in trials was 18-year old. Supplementation with *NS* oil can significantly improve lipid profile in hyperlipidemic patients with T2DM (Heshmati *et al.*, 2015; Kaatabi *et al.*, 2012; Ahmed *et al.*, 2012), with menopausal women (Ibrahim *et al.*, 2014), with metabolic syndrome (Najmi *et al.*,

et al., 2012; Najmi *et al.*, 2008), and with coronary heart disease (Tasawar *et al.*, 2011). However, no complications caused by *NS* were observed in all studies (Table 2).

DISCUSSION

In this systematic review we have tried to evaluate the effects of *Nigella sativa* supplementation on lipid profile in hyperlipidemia accompanied with many conditions. Lipid profiles constitute one of the most important factors that can be changed in many diseases and are used to evaluate conditions of the patients and subjects (Mohtashami and Entezari, 2016). In our review, *Nigella sativa* supplement can change lipid profiles significantly in different conditions (Heshmati *et al.*, 2015; Ibrahim *et al.*, 2014; Qibi *et al.*, 2006; Najmi *et al.*, 2012; Tasawar *et al.*, 2011; Kaatabi *et al.*, 2012; Najmi *et al.*, 2008; Bhatii *et al.*, 2009; Sabzghabae *et al.*, 2012; Datau *et al.*, 2010; Qidwai *et al.*, 2009; Dehkordi *et al.*, 2008; Bamosa *et al.*, 1997; Ahmed *et al.*, 2012).

In one trial study (Heshmati *et al.*, 2015) reported that *NS* oil decreased LDL-C and TG levels after 3 months while other previous studies reported different effects of *NS* on lipid

parameters. Kaatabi *et al.* (2012) evaluated different dosages of powdered NS (1, 2 and 3 g/day) in patients with type 2 diabetes. They indicated that 1 g/day NS increased HDL-C levels after 12 weeks. Two and 3 g/day of black seed decreased TC, TG and LDL-C levels and increased HDL-C concentration. However another study used supplementation with NS powder concurrent with aerobic training program decreased TC, LDL-C, TG and increased HDL-C in overweight females after 8 weeks (Heshmati *et al.*, 2015; Farzaneh *et al.*, 2014). Najmi *et al.*, 2008 reported that 2.5 ml NS oil decreased TC and LDL-C levels with no changes in HDL and TG concentrations (Farzaneh *et al.*, 2014). These mentioned studies indicated positive effects of NS on lipid profile, but differences in dose and type of NS, dietary intake, physical activity level, baseline lipid profile, duration of intervention, type of disease, ethnicity and genotype may lead to different results.

In another trial the hypolipidemic effects of *N. sativa* was studied in menopausal women as part of the increasing drive to provide better insights into the effects of plant bioresources on health, and their potential use for therapy of chronic diseases (Ibrahim *et al.*, 2014). Also, increasing numbers of women are thought to use complementary medicines for disorders associated with their menopause, and studies like these could provide evidence-based rationale for their choice of plant bioresources (Ibrahim *et al.*, 2014). Specifically, about 75% of women were reported to be using herbal and complementary medicines in their menopausal period in place of hormone replacement therapy due to considerations on its side effects (Ibrahim *et al.*, 2014; Tong IL, 2013).

Current study showed highly significant results noted on the lipids on healthy subjects (Qibi *et al.*, 2006). These results support the benefit of a simple dietary element in improving lipid profile in normal people. *Nigella sativa* was shown to reduce TC, LDL-C and TG, while increasing HDL-C. All these effects are in favor of reducing the risks of atherosclerosis (Qibi *et al.*, 2006; Nickavar *et al.*, 2003).

The fatty acid composition of the black seed, including a predominance of linoleic acid (n6 polyunsaturated fatty acid) (Qibi *et al.*, 2006; Hassanien, 2004), may explain its lipid lowering activity. Epidemiological and clinical studies have established that n6 fatty acids protect against CHD (Morikawa, 2004). These favorable results on normal people should stimulate a further work on large number of persons and in studying the effect of *N. sativa* as a lipid lowering remedy in dyslipidaemic patients on a wider scale (Qibi *et al.*, 2006). Current study revealed the effect of *Nigella sativa* on FBG, PPBG, HbA1C & lipid profile of metabolic syndrome patients with poor glycemic control (HbA1C > 7 %) (Najmi *et al.*, 2012). Reduction in FBG, PPBG, HbA1C were more (P value < 0.001) in *Nigella sativa* group as compared to standard group. Significant improvement in HbA1C indicates that *Nigella sativa* can be used as add on therapy to those patients whose glycemic control cannot be achieved by conventional drugs. Reduction in LDL cholesterol was more (P value < 0.001) in *Nigella sativa* group (NS) as compared to standard group (Najmi *et al.*, 2012). These results were the same as reported previously in

various studies. Insulin resistance leads to the overproduction of very low density lipoproteins (VLDLs) and to reduced lipoprotein lipase activity, thereby resulting in dyslipidemia. Therefore, attainment of better glycemic control may improve the lipid profile (Najmi *et al.*, 2012). The presence of various unsaturated fatty acids like Arachidonic, eicosadienoic, linoleic, linolenic, oleic and almitoleic acid (Najmi *et al.*, 2012; El. D. M *et al.*, 2000), may be responsible for the improvement of lipid profile. The various mechanisms were proposed for the lowering of cholesterol. The seeds may either inhibit de novo cholesterol synthesis or stimulate bile acid excretion. It is well-known that both effects would lead to a decrease in serum cholesterol (Najmi *et al.*, 2012; Beynen *et al.*, 1987). These results confirmed that *Nigella sativa* can be used as add on drug therapy in patients of metabolic syndrome with poor glycemic control (Najmi *et al.*, 2012).

The cholesterol lowering effect of *N. sativa* may be attributed to the presence of phyosterols 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 (Sabzghabae *et al.*, 2012, De Jong *et al.*, 2003); it may also activate LDL-receptor by decreasing intracellular cholesterol, which leads to rapid clearance of LDL-cholesterol from blood circulation (Bamosa *et al.*, 1997). The effect of *N. sativa* on increasing cholesterol secretion in the bile is another probable mechanisms which can enhance its cholesterol lowering properties (Ibraheim Z, 2002).

Although Bamosa *et al.*, 1997, 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 but there was no significant decrease in triglyceride level (Bamosa *et al.*, 1997).

CONCLUSION

This systematic review on 14 studies demonstrated that *Nigella sativa* supplement in different doses and durations can improve lipid profiles in humans either with hyperlipidemia alone or associated with other conditions as diabetes mellitus and metabolic syndrome. However, the effect of this supplement is more pronounced on levels of TC, LDL, than on TG, HDL. Therefore, it is suggested that consumption of *Nigella sativa* supplementation be considered as a complementary treatment protocol for many diseases, especially hyperlipidemia and metabolic disorders. Although, NS can be used as a complementary therapies in cases related to hyperlipidemia, but due to differences in models, chemical compositions of difference sources of NS, dosage, and duration of intervention, it is difficult to determine effective type and dosage of NS. More studies are suggested to clarify effective type and dosage of NS in patients with hyperlipidemia.

ACKNOWLEDGEMENT

The authors would like to express appreciation to all reviewers who have been worked hardly to help authors in reading

and classification of the articles and for their support in this review.

Financial support and sponsorship: Nil.

Conflict of Interests: There are no conflicts of interest.

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How to cite this article:

Al-Naggar RA, Osman MT, Mohamed IN, Aripin KNB, Abdulghani MAM. Effect of *Nigella sativa* supplementation on human lipids: systematic review. *J App Pharm Sci*, 2017; 7 (04): 213-219.