Review Article

# *Nigella sativa* in controlling Type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases: Molecular aspects

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Oxidative stress is an important factor in the etiology of several chronic diseases that include cardiovascular disease (CVD), Type 2 diabetes (T2D), and rheumatoid arthritis (RA). Oxidative stress can lead to inflammation, and this can contribute to these chronic diseases. Reducing inflammation and oxidative stress may, therefore, be useful in the prevention and treatment of these conditions. One of the treatment options for chronic diseases is the use of traditional medicine and herbs, such as *Nigella sativa*. This is one of the herbs that have recently been assessed for its ability to reduce inflammation and oxidative stress. We have reviewed the reported effects of *N. sativa* on risk factors of chronic diseases (CVD, DM, and RA) with emphasis on molecular and cellular mechanisms in controlling inflammation and oxidative stress. Various mechanisms have been proposed to contribute to the beneficial properties of *N. sativa*, including a reduction of lipid peroxidation via its antioxidant properties; agonist of peroxisome proliferator-activated receptor gamma in adipose tissue; activation of AMP-activated protein kinase, increased antioxidants, inhibition of nuclear factor-kappa B pathway; increased in interleukin-10 expression, CD4+ T-cell percentage, T regulatory cell percentage (CD4+ CD25+ T-cell) in peripheral blood, and CD4+/CD8+ ratio, but to prove this claim, it is necessary to conduct experimental and well-designed clinical trial studies with a larger sample size on the effects of *N. sativa* on these chronic diseases.

**Key words:** Chronic disease, inflammation, *Nigella sativa*, oxidative stress

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## INTRODUCTION

CChronic diseases may be defined as a long-term illness with long treatment period that cannot currently be prevented by vaccines, or fully cured by medication and also causes physical changes in the body and reduces its performance.[1] According to the Centers for Disease Control (CDC) definition, cardiovascular disease (CVD), Type 2 diabetes (T2D), and rheumatoid arthritis (RA) are common chronic diseases globally.[1,2] CVD is

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associated with dysfunction of the heart and blood vessels and comprises disorders such as coronary heart disease and hypertension.[3] It has been estimated that the prevalence of hypertension and CVD reaches about 30% of the world's population by the year 2025.[4-6] T2D is the most common type of diabetes, accounting for 90% of all diabetes cases.[7] The number of people with T2D in the world was estimated to be approximately 125 million in 1997 and is expected to reach 300 million by 2025, and on average, the prevalence among adults is 8.5%.[8,9] RA is an autoimmune chronic disease that affects the small joints of the human body and affects approximately 1% of the population and is usually associated with severe disability.[10] Based on the National Health Council (NHC) reports, the burden of the cost of chronic diseases annually in the United States is about $ 1.3 trillion for seven common chronic diseases and now about 78% of total health care spending in the United States is spent on chronic diseases, and this trend is increasing.[11] It has been widely accepted that persistent oxidative stress leads to chronic inflammation and this inflammation can be effective in many chronic diseases such as CVD, T2D, and RA;[12] therefore, it is possible that reducing the level of inflammation and oxidative stress may ameliorate these diseases. One of the treatment options for chronic diseases is the use of traditional medicine and herbs, and it has been shown to be used in both prevention and treatment.[13] In general, the consumption of medicinal plants is increasing in different countries due to the evidence of the positive effects as well as the low side effects and availability of these plants.[14-16] *Nigella sativa* is one of the herbs that have recently been used to reduce inflammation and oxidative stress in various chronic diseases.[17]

*N. sativa* is also known as black seed, black cumin, habbatus sauda, and black caraway seed. It is cultivated in countries such as India, Pakistan, and some parts of Iran. The plant is a local herb in southern Europe, North Africa, and Asia.[18-21] *N. sativa*, as a 1-year-old plant, has flowers whose stem is covered with very delicate fluff and grows to a height of 20–30 cm; this plant's flowers are solitary and pale blue or white with 5 petals, the fruits are shaped like a large capsule containing 3–7 follicles, and the seeds in each follicle are black in color and have a bitter, spicy flavor[22] [Figure 1].

**Figure 1:** *Nigella sativa* plant: Fruits, leaf, and flowers

*N. sativa* has been reported to contain more than 100 chemical compounds and has many reported therapeutic effects due to these compounds. *N. sativa* oil contains average, 35.6%–41.6% fat (constant oil), 22.7% protein, 32% carbohydrate, and 0.5%–1.6% essential fatty acid. The major fatty acid in this plant is linoleic acid (about 57.3% of fixed oil).[23,24] It also contains other compounds such as crude fiber, reducing sugars, mucilage, resin, alkaloids, sterols, tannins, flavonoids, saponins, minerals (such as Fe, zinc, Na, phosphorus, and calcium), and vitamins (C, B1, B3, B6, and B9 as water-soluble vitamins and A and E as a couple of fat-soluble vitamins).[24,25] The biological activity of *N. sativa* is attributed to the following proportions of forming components: volatile oils, such as thymoquinone (TQ) (30%–48%), P-cymene (7%–15%), carvacrol (6%–12%), 4-terpineol (2%–7%), trans-anethole (1%–4%), and sesquiterpene longifolene (1%–8%). A combination of four monoterpenes (d-limonene (carvone), carvone, pinene-α, and p-cymene), TQ, and its derivatives are the most pharmacologically active compounds.[24,26,27] TQ is not only a type of inhibitor for chemically reactive species containing oxygen such as superoxide and hydroxyl radicals but also inhibits leukotriene C4 and B4 production in humans and has anti-inflammatory effects.[27,28]

Recent studies have shown that *N. sativa* can be helpful and effective in the prevention and treatment of some chronic diseases, such as asthma, liver and kidney disease, influenza, and gastrointestinal problems.[21,29] Previous studies reported that *N. sativa* was used as antihypertensive, liver tonics, diuretics, antidiarrheal, appetite stimulant, analgesics, digestive, antibacterial, and in skin disorders,[30] and also, its effects on neurological and mental illness, cardiovascular disorders, cancer, diabetes, and inflammatory conditions have been shown.[31] Effects of an aqueous extract from *N. sativa* on glucose tolerance and body weight in rats were studied by Meddan *et al*.[32] In a similar study, *N. sativa* was reported to reduce the risk of CVD in diabetic patients.[33] Some studies have also shown the anti-inflammatory and analgesic effects of *N. sativa* in RA.[34]

Despite the effects of *N. sativa* on some chronic disease risk factors in previous studies, the exact mechanism of these effects has not been identified and the results of some studies have been inconsistent. Therefore, this study aims to review the possible molecular and cellular effects of *N. sativa* on inflammation, oxidative stress, and other related risk factors of chronic diseases (CVD, T2D, and RA).

## SEARCH STRATEGY

PubMed-Medline, Google Scholar, Scopus, and Web of Science databases were searched to identify the relevant articles. The keywords including "nigella sativa," OR "black

seed," OR "black cumin," OR "habbatus sauda," OR "black–caraway seed" in combination with "diabetes," "insulin resistance," "glucose," "hemoglobin A1C," "dyslipidemia," "lipid profile," "blood pressure," "cardiovascular disease," "heart disease," "rheumatoid arthritis," "atherosclerosis," "oxidative stress," "anti-oxidant," "inflammation," and "inflammatory markers" were used for an electronic search strategy. All the identified studies and review articles were reviewed. Subsequently, the eligible experimental and clinical trials were selected. These are papers reporting original studies on the mechanisms of action of *N. sativa* and almost all available animal and human studies. However, we mentioned that this study is a narrative review and not in a systematic framework.

## EFFECTS OF *NIGELLA SATIVA* IN CARDIOVASCULAR RISK FACTORS

### Laboratory animal studies

Three doses of hydroalcoholic extract of *N. sativa* (200, 400, and 600 mg/kg) were injected intraperitoneally in hypertensive rats showed a protective effect on blood pressure (BP) after 30 min of injection that was induced by TQ and its effects on angiotensin II.[35] In another study, improvements of cardiovascular risk factors including body weight, red blood cell and white blood cell, lipid profile (triglyceride [TG], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) and immune response (IgM and IgG), total antioxidant capacity, and malondialdehyde (MDA) after 8-week supplementation with *N. sativa* seed at doses of 300 and 600 g/kg in rabbits were proved.[36] This effect was dose dependent. The cardioprotective effects of *N. sativa* are summarized in Table 1.

### Clinical studies

Clinical trials in human subjects showed similar results. Sabzghabaee *et al*.[37] have reported that 2 g/d *N. sativa* for 4 weeks in hyperlipidemic patients significantly reduced total cholesterol (TC), TG, and LDL compared to control group [Table 2]. Furthermore, 500 mg/d *N. sativa* in metabolic syndrome patients decreased systolic and diastolic BP and LDL-cholesterol (LDL-C) compared to control group.[38]

### Effect on lipid profile

Improvements in serum lipid profile were investigated in human and animal studies. The meta-analysis on the effect of *N. sativa* on lipid profiles indicated that the levels of TC and LDL-C dropped significantly.[39,40] Sahebkar *et al*. showed significant reductions in serum TG.[40] Daryabeygi-Khotbehsara *et al*.[39] found that *N. sativa* seed oil reduced serum TG, while seed powder increased TG levels what may be a consequence for different preparation processes of crushed seeds and extracted oil in addition to chemical composition.[39] Another systematic review revealed that *N. sativa* supplementation might be effective in glycemic control, but its effects on anthropometric parameters and lipid profile were controversial.[41]

The effects of *N. sativa* on lipid profile may be related to its antioxidant properties,[42] and its agonist effects on peroxisome proliferator-activated receptor gamma (PPAR-γ),[43] reducing lipid peroxidation,[42] upregulation of the LDL receptor in the hepatocytes subsequently, cholesterol removal, and suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA R) gene and cholesterol synthase.[44]

### Effect on blood pressure

*N. sativa* lowers BP sharply according to meta-analysis.[45] This may be connected to some factors such as diuretic effect, calcium channel-blocking properties, and cardiac depressant effect of *N. sativa* that are likely related to various components of *N. sativa* involved in this effect, including TQ, and fatty acids that contain substantial quantities of linoleic, oleic, and arachidonic acids, nigellicine, flavonoids, trans-anethole, p-cymene, α-pinene, limonene, carvone, and soluble fiber[41,46] volatile oils extracted from *N. sativa* and TQ may directly or indirectly reduce both BP and heart rate, by their serotoninergic and muscarinic properties.[47] *N. sativa* compounds are also reported to have endothelium-independent relaxation effects that may be due to suppression of $Ca^{2+}$ release from the sarcoplasmic reticulum across the smooth muscle cell membrane and reduction of $Ca^{2+}$ sensitivity and influx.[48] Furthermore, *N. sativa* may reduce BP by its diuretic effects and regulate the electrolytes and water content, and also control of blood volume; subsequently, cardiac output is reduced, an important regulator of BP.[49] Figure 2 shows the potential mechanisms of the effect of *N. sativa* on CVD.

## EFFECTS OF *NIGELLA SATIVA* IN TYPE 2 DIABETES

### Laboratory animal studies

T2D mellitus is marked by hyperglycemia, dyslipidemia and increased oxidative markers that may be caused insulin resistance, and finally, overt diabetes.[50] Seeds of *N. sativa* have been used as a natural treatment for various diseases. Hypoglycemic, hypolipidemic, and antioxidant effects of *N. sativa* have been reported.[51-53] Numerous studies have been done in diabetic animal models. El-Dakhakhny *et al*. have shown that 0.4 g/kg *N. sativa* oil significantly diluted blood glucose concentration in diabetic rats after 6 weeks.[54] Insulin levels in diabetic rats treated with a dose of 20 ml/kg aqueous extract of *N. sativa* rose after 15 days.[55] Houcher *et al*. reported that intraperitoneally, a daily dosage of 810 mg/kg methanol extract and 2.5 ml/kg of *N. sativa* oil not only lowered glucose but also increased total antioxidant capacity levels in diabetic rats after treated for 25 days.[56] Kantar *et al*. showed that 50 mg/kg TQ administered orally grew both energy

**Table 1: Effects of *Nigella sativa* on cardiovascular, diabetes, and rheumatoid arthritis risk factors in experimental studies**

| Author (year) | Country (reference number) | *n* | Type and dose of N.S administered | Duration | Outcome measures |
|---|---|---|---|---|---|
| Enayatfard *et al*. (2019)[35] | Iran | 21 hypertensive rats | 200, 400, and 600 mg/kg N.S | Once injection | Dose-dependent reduction in systolic blood pressure, mean arterial pressure, and heart rate |
| El-Gindy *et al*. (2019)[36] | Egypt | 54 growing V-line unsexed rabbits | 300 or 600 mg of N.S seed/kg | 8 weeks | Significantly improved body weight, ↑RBCs and WBCs ↑IgG and IgM immune responses, ↓ serum total lipids, TG, LDL, and MDA, and ↑HDL and total antioxidant capacity. |
| Ahmed and Hassanein (2013)[94] | Egypt | 45 Albino rats | N.S oil (4 ml/kg) orally | Once administration | ↓heart rate, ST-segment change, pro-inflammatory cytokines, oxidative stress, and cardiac tissue damage |
| Randhawa (2013)[95] | India | 16 Wistar albino rats | 0.2 ml/kg/day, intraperitoneally | 6 weeks | ↓blood pressure, oxidative injury, improved left ventricular function |
| Babaei Bonab and Tofighi (2019)[96] | Iran | 35 male Wistar rats with T2M | 400mg/kg/day | 8 weeks | Improvement in lipid profile (LDL, HDL, TC, and TG), FBG, HbA1c, and insulin resistance |
| Ahmad and Alkreathy (2018)[97] | Saudi Arabia | 48 male Albino Wistar rats | 2 ml/kg, p.o | 7 days | Improvement in lipid profile (TC, LDL, HDL, and TG) |
| Muneera *et al*. (2015)[98] | Pakistan | 30 Sprague Dawley rats | 1000mg/kg/day | 6 weeks | Improvement in the lipid profile of rats |
| Al-Hader *et al*. (1993)[99] | Jordan | Diabetic rabbits | 50 mg/kg volatile oil extract of N.S | 2, 4, and 6 h | Showed significant decreases in FBG levels |
| Meral *et al*. (2001)[44] | Turkey | 15 New Zealand male rabbits | 20 ml/kg aqueous extract of N.S | 2 months | ↑GSH and ceruloplasmin concentrations ↓MDA and glucose levels |
| El-Dakhakhny *et al*. (2002)[54] | Egypt | Diabetic rats | 0.4g/kg N.S oil | 2, 4, and 6 weeks | ↓blood glucose concentration |
| Kanter *et al*. (2003)[59] | Turkey | 46 male Wistar rats | 0.2 ml/kg/day volatile oil of N.S | 4 weeks | ↓GSH, glucose level, and serum NO ↑Insulin level |
| Fararh *et al*. (2004)[74] | Japan | Male Syrian hamsters | 400 mg/kg body weight/ day of N.S oil | 4 weeks | ↓total glycated hemoglobin |
| Rchid *et al*. (2004)[61] | - | Rat pancreatic cells | 0.01, 0.1, 1, and 5 mg/ml whole, basic, and acidic subfractions of N.S | 30 min | A significant stimulatory effect on insulin release has been observed |
| Mansi *et al*. (2005)[55] | Jordan | Diabetic rats | 20 ml/kg/day aqueous extract of N.S | 15 days | ↑Insulin level and ↓Glucose level |
| Mansi (2006)[100] | Jordan | Diabetic rats | 20 ml/kg aqueous extract of N.S | 3 weeks | ↑Insulin level |
| Kaleem *et al*. (2006)[101] | India | Wister rats | 300 mg/kg/day ethanol extract of N.S | 4 weeks | ↑Catalase, SOD and insulin levels ↓Lipid peroxidation, GPX and glutathione ↓Body weight |
| Houcher *et al*. (2007)[56] | Algeria | Diabetic rats | 810 mg/kg/day 2.5 ml/kg/day methanol extract of N.S and N.S oil | 25 days | ↓Glucose level ↑TAC |
| Kanter (2008)[58] | Turkey | diabetic rats | N.S in a dose of 400 mg/kg body weight and TQ 50 mg/kg body weight once a day | 12 weeks | ↓Serum glucose |
| AL-Logmani (2009)[102] | Saudi Arabia | 40 diabetic male Wistar rats | N.S oil | 3 weeks | ↓Blood glucose |
| Meddah *et al*. (2009)[59] | Morocco | Rat jejunum | *In vitro*: 0.1 pg/ml to 100 ng/ml *In vivo*: 2g/kg | 6 weeks | *In vivo*: glucose tolerance and body weight improvement *In vitro*: inhibition of glucose absorption |

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**Table 1: Contd...**

| Author (year) | Country (reference number) | *n* | Type and dose of N.S administered | Duration | Outcome measures |
|---|---|---|---|---|---|
| Benhaddou-Andaloussi *et al*. (2010)[103] | Morocco | C2C12 skeletal muscle cells and 3T3-L1 adiposities | Ethanol extract of N.S | 18 h | ↑Glucose uptake in skeletal cells and adiposities |
| Fararh *et al*. (2010)[53] | Egypt | Diabetic rats | 50 mg/kg/day TQ | 20 days | ↓ Plasma glucose, TC, TG<br>↑ Insulin concentration |
| Abdelmeguid *et al*. (2010)[62] | Egypt | Diabetic rats | 2 mL/kg, i.p., 5% N. S Extract 0.2 mL/kg, i.p, N.S oil, or 3 mg/mL, i.p., TQ | 30 days | ↓ glucose and improve serum insulin levels |
| Salama (2011)[52] | Saudi Arabia | Diabetic rats | 500 mg/kg N.S oil | 4 weeks | ↓Glucose concentration<br>↑insulin, c-peptide, and TAC |
| Al-Logmani and Zari (2011)[104] | Saudi Arabia | Diabetic Wistar rats | Diet containing 5% N.S oil | 7 weeks | *N. sativa* oil decreased blood glucose levels<br>↑ HDL; ↓TG, LDL |
| Alimohammadi *et al*. (2013)[105] | Iran | Diabetic rats | 5, 10, and 20 mg/kg hydroalcoholic N.S extract | 32 days | 5 mg/kg: ↓FBS<br>↑Insulin secretion |
| Mohamed *et al*. (2015)[51] | Saudi Arabia | Nonalcoholic fatty liver in obese diabetic albino rats | 100mg/kg aqueous extract of N.S seed | 4 weeks | ↓FBS<br>↓TG, TC |
| Asaduzzaman *et al*. (2015)[106] | Bangladesh | Diabetic rats | 300 mg/kg body weight of ethanol extract of N.S | 28 days | ↓TG, TC, LDL, and FBG<br>↑HDL |
| Al-Trad *et al*. (2016)[107] | Jordan | Experimental diabetic rats | 50 mg/kg TQ and 2 mL/kg N.S oil | 10 weeks | N.S oil or TQ significantly reduced blood glucose level compared with that in untreated diabetic rats |
| Umar *et al*. (2012)[75] | India | Three groups of six Wistar albino rats each with collagen-induced arthritis | 5 mg/ kg TQ PO | 21 days | ↓ IL-1β, IL-6, TNF-α, IFN- γ, PGE2, articular elastase, myeloperoxidase, lipoxygenase, and NO<br>↑IL-10, SOD, GPX, and catalase |
| Vaillancourt *et al*. (2011)[76] | Canada | 24 female Lewis rats with lipopolysaccharide (LPS)-induced arthritis | 5 mg/ kg TQ PO | 7 days | ↓ LPS-induced IL-1β, TNF-α, MMP-13, Cox-2, and PGE2 |
| Tekeoglu *et al*. (2006)[108] | Turkey | Five groups of seven Wistar albino rats each with collagen-induced arthritis | 2.5 mg/kg and 5 mg/kg TQ PO | 7 days | ↓ TNF-α and IL-1β |
| Mohamed *et al*. (2003)[109] | Canada | 24 mice with inducing inflammation | 1 mg/kg TQ iv | 5 days and 12 days | Mice received TQ at day 12:<br>Higher levels of GSH<br>Significant reduction of symptoms of inflammation |
| Faisal *et al*. (2015)[110] | Pakistan | 32 rats with collagen-induced arthritis | 2mg/kg/day TQ by i.p injection | 15 days | ↓ in clinical score of inflammation and differentiation leucocyte counts |
| Zhong (2017) | China | 60 rabbit osteoarthritis model | 1mg/kg/day TQ by intra-articular injection | 9 weeks | ↓ in MMP-13 mRNA and cartilage lesions |
| Chen *et al*. (2010)[111] | China | 20 rabbit osteoarthritis model | 10 μmol/L TQ intra-articular injection | 4 weeks | Inhibited NF-kB p65<br>↓ IL-1β<br>Suppressed the MMP-1, MMP-3, and MMP-13 gene expression |

N.S=*Nigella sativa*; TQ=thymoquinone; i.p=intraperitoneal; RBC=Red blood cells; WBC=White blood cells; TG=Triglyceride; TC=Total cholesterol; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; MDA=Malondialdehyde; IgG=Immunoglobulin G; IgM=Immunoglobulin M; FBG=Fasting blood glucose; HbA1C=Glycated hemoglobin; IL-1β=Interleukin-1 beta; IL-6=Interleukin-6; TNF-α=Tumor necrosis factor-alpha; IFN- γ=Interferon-gamma; PGE2=Prostaglandin E2; GSH=Glutathione; NO=Nitric oxide, GPX=Glutathione peroxidase; TAC=Total antioxidant capacity; IL-10=Interleukin-10; LPS=Lipopolysaccharide; MMP=Matrix metalloproteinase; Cox-2=Cyclooxygenase 2; NF-kB=Nuclear factor-κB

metabolism and insulin levels in diabetic rats after 20 days of insertion.[57-59] These studies also showed that a single daily dosage of 400 mg/kg and 50 mg/kg body weight *N. sativa* and TQ, respectively, administered orally in diabetic rats decreased serum glucose after the intervention.[58] Salama *et al*. in an animal study reported that oral 500 mg/kg *N. sativa*

**Table 2: Effects of *Nigella sativa* on cardiovascular, diabetes, and rheumatoid arthritis risk factors in clinical trial studies**

| Author (year) | Country (reference number) | Study design (sex) | Participant numbers | Type and dose of N.S administered | Duration (mean age of subjects) | Outcome measures |
|---|---|---|---|---|---|---|
| **Cardiovascular risk factors** | | | | | | |
| Darand *et al*. (2019) [112] | Iran | RCT (male/female) | 50 patients with NAFLD | 2 g/day | 12 weeks | ↓serum glucose and serum insulin<br>↑quantitative insulin sensitivity |
| Sabzghabaee *et al*. (2012)[37] | Iran | RCT (male/female) | 88 Hyperlipidemia patients | 2 g/d (capsule contained N.S crushed seeds) | 4 weeks | ↓TC, TG, and LDL, no significant difference in HDL, FBG |
| Dehkordi and Kamkhah (2008)[113] | Iran | RCT (male/female) | Patients with mild hypertension | Two test groups received 100 and 200 mg of N.S extract twice a day | 8 weeks | Significant dose-dependent decline in the levels of TC, TG, LDL, systolic and diastolic blood pressure |
| Najimi *et al*. (2013) [38] | India | Open labeled RCT (male/female) | 90 patients of metabolic syndrome | 500 mg capsule of N.S per day | 8 weeks | Significant improvement with reference to systolic and diastolic blood pressure and LDL-cholesterol, no significant difference in HDL, TG |
| Ibrahim *et al*. (2014) [114] | Malaysia | RCT (female) | 37 hyperlipidemic menopausal women | 500 mg capsule of N.S per day | 2 months | ↓ TC, LDL and TG, and increased HDL and FBG. No significant difference in diastolic and systolic blood pressure |
| Tasawar *et al*. (2011) [115] | Pakistan | RCT (male/female) | 80 patients with coronary artery diseases | 500 mg capsule of N.S per day | 6 months | ↓TC, LDL, VLDL, and TG<br>↑HDL-C |
| Bamosa *et al*. (1997) [116] | Saudi Arabia | CT (male) | 16 male adolescents | 2 capsules of 500 mg N.S twice daily | 2 weeks | ↓ glucose<br>No significant difference for TG change |
| Farzaneh *et al*. (2014)[117] | Iran | RCT (female) | 20 sedentary overweight females | 3 capsules of 500 mg N.S daily | 8 weeks | ↓TC, LDL, TG, and body mass index, and ↑HDL-C |
| Najimi *et al*. (2008) [118] | India | CT (male/female) | 60 patients of metabolic syndrome | N.S oil 2.5 ml twice daily | 6 weeks | ↑TC, LDL, FBG<br>No effect on TG, HDL, postprandial glucose, body weight, BMI, and waist circumference |
| Mahdavi *et al*. (2015)[119] | Iran | RCT (female) | 90 obese women | 3 g per day (1 g before each meal) N.S oil | 8 weeks | ↓VLD, TG, and BMI<br>No effect on HDL, TC, and LDL |
| Rashidmayvan *et al*. (2019)[66] | Iran | RCT (male/female) | 44 patients with NAFLD | N.S oil | 8 weeks | ↓FBS, TG, TC, LDL, VLDL, AST and ALT, hs-CRP, IL-6, TNF-α<br>↑HDL-C<br>N.S oil had no significant effect on serum levels of insulin, blood pressure, and GGT |
| Pelegrin *et al*. (2019)[69] | France | Pilot RCT (male) | 30 healthy male volunteers | N.S powder (1 g/day) | 4 weeks | ↓TC, LDL |
| Farhangi *et al*. (2018)[120] | Iran | RCT (male/female) | 40 patients with Hashimoto's thyroiditis | 2 g N.S powder per day | 8 weeks | ↓ BMI, LDL, and TG<br>↑ HDL |
| Bhatti *et al*. (2016)[121] | Pakistan | CT (male/female) | 60 hyperlipidemic smokers | 1 g of N.S (kalonji) seed | 30 days | ↓TC, LDL, and TG, ↑ HDL |
| **Diabetes risk factors** | | | | | | |
| Bamosa *et al*. (2010)[64] | Saudi Arabia | RCT (male/female) | 94 patients with T2D | Capsules containing N.S (1, 2, and 3 g/day) | 12 weeks | ↓ FBS, 2hPG, and HbA1c |

*Contd...*

**Table 2: Contd...**

| Author (year) | Country (reference number) | Study design (sex) | Participant numbers | Type and dose of N.S administered | Duration (mean age of subjects) | Outcome measures |
|---|---|---|---|---|---|---|
| **Diabetes risk factors** | | | | | | |
| Kaatabi *et al*. (2012) [122] | Saudi Arabia | 94 diabetic patients | CT (F) | 1, 2, and 3 g/day of powdered N.S | 12 weeks | 1gr: ↑HDL-C<br>2gr: ↑ HDL; ↓TC, TG, and LDL-C; 3gr: ↑HDL; ↓ TC, TG, and LDL-C |
| Hosseini *et al*. (2013)[123] | Iran | RCT (male/female) | 70 patients with T2D | 5 ml/day N.S oil | 12 weeks | ↓FBS, 2hPG, BMI |
| Mirmiran *et al*. (2015)[68] | Iran | RCT (male/female) | 43 patients with T2D | 1000 mg extract of black seed oil | 8 weeks | ↓FBS, LDL, total cholesterol, and LDL/HDL |
| Heshmati *et al*. (2015)[124] | Iran | RCT (male/female) | 72 patients with | 3 g/day N.S oil or soft gel capsules | 12 weeks | ↓FBS, HbA1c, ↓LDL-C, and TG |
| Farhangi *et al*. (2018)[120] | Iran | RCT (male/female) | 40 patients with Hashimoto's thyroiditis | 2 g N.S powder per day | 8 weeks | ↓BMI<br>↑HDL<br>↓Serum concentrations of LDL and tri-TG |
| Rashidmayvan *et al*. (2019)[66] | Iran | RCT (male/female) | 44 patients with NAFLD | 1000 mg N.S oil per day | 8 weeks | ↓ FBS level<br>↓TG, TC, LDL, VLDL<br>↑ HDL |
| Pelegrin *et al*. (2019) [69] | France | Pilot RCT (male) | 30 healthy male volunteers | N.S powder (1 g/ day) | 4-weeks | Ineffective on glucose-induced insulin secretion and insulin sensitivity |
| **Rheumatoid arthritis risk factors** | | | | | | |
| Hadi *et al*. (2016)[77] | Iran | RCT (female) | 45 patients with rheumatoid arthritis | two capsules 500 mg/day N.S oil | 8 weeks | ↓ MDA, NO<br>↑ Serum level of IL-10 |
| Kheirouri *et al*. (2016)[91] | Iran | RCT (female) | 45 patients with rheumatoid arthritis | two capsules 500 mg/day N.S oil | 8 weeks | ↓ hs-CRP level, cytotoxic T-cells (CD8+), DAS-28 score, and an improved number of swollen joints.<br>↓ Serum level of CD4+ T-cell percentage, T regulatory cell percentage (CD4+CD25+ T-cell) and CD4+/CD8+ ratio |
| Gheita and Kenawy (2012)[78] | Egypt | RCT (female) | 40 patients with rheumatoid arthritis | Two capsules 500 mg/day N.S oil | 4 weeks | ↓DAS-28, joint inflammation, and morning stiffness |
| Kooshki *et al*. (2016) [125] | Iran | RCT (male/female) | 40 elderly patients with knee osteoarthritis | Topical application of 3cc N.S oil on knee | 3 weeks | Pain reduction in the black seed group was greater than that of the acetaminophen group |

N.S=*Nigella sativa*; RCT=Randomized controlled trial; TG=Triglyceride; TC=Total cholesterol; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; VLDL=Very-low-density lipoprotein; FBG=Fasting blood glucose; BMI=Body mass index; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; GGT=Gamma-glutamyltransferase; hs-CRP; high-sensitive C-reactive protein; IL-6=Interleukin-6; TNF-α=Tumor necrosis factor-α ; T2D=Type 2 diabetes; FBS=Fasting blood sugar; 2hPG=2-h postprandially glucose; HbA1c=Glycosylated hemoglobin; NAFLD=Nonalcoholic fatty liver disease; MDA=Malondialdehyde; NO=Nitric oxide; DAS-28=Disease Activity Score-28

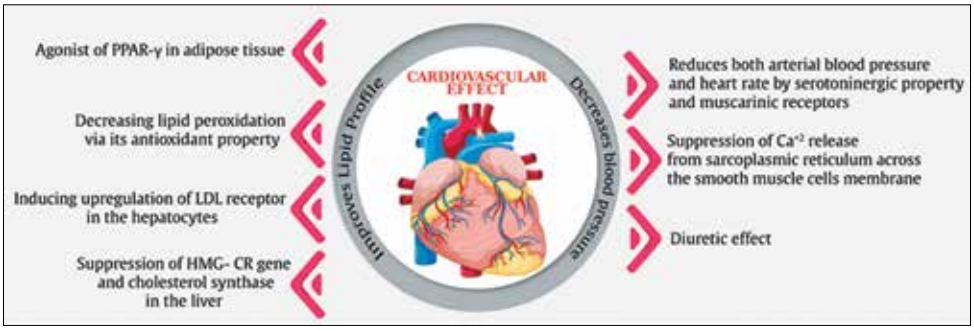


**Figure 2:** Potential mechanisms of the effect of N. sativa on cardiovascular disease. PPAR-γ = Peroxisome proliferator-activated receptor gamma; LDL receptor = Low-density lipoprotein receptor; HMG-CR = 3-Hydroxy-3-methylglutaryl-coenzyme A reductase

oil increased serum C-peptide, insulin, and total antioxidant capacity (TAC) concentration and decreased glucose level in a diabetic rat model.[52] Some studies assert that these antidiabetic properties of *N. sativa* are due to insulinotropic action,[60,61] hepatic gluconeogenesis inhibition, and its antioxidant effects.[52,56,62,63] Many studies have been done to confirm the properties of *N. sativa* on insulin sensitivity and release.[55] Several attempts have been worked on *N. sativa,* and they suggest that this plant improves insulin sensitivity by preventing the severity of oxidative stress. Insulin secretory effects of *N. sativa* have been probed on *in vitro* isolated rat pancreatic islets and saw that the secretion of insulin is increased in the presence of *N. sativa*. Table 1 summarizes the effects of *N. sativa* on diabetes in experimental studies.

### Clinical studies

There have been several clinical studies that have evaluated the effects of oral *N. sativa* supplementation in different subject groups. Bamosa *et al*. in a clinical trial on 94 patients with diabetes showed that 2 g/day of *N. sativa* seed supplementation decreased fasting blood glucose (FBG), 2 h postprandially glucose, glycosylated hemoglobin (HbA1c), and insulin resistance after 12 weeks.[64] Hosseini *et al*. have reported a significant decrease in FBG, 2 h postprandial glucose, and HbA1c in 70 patients with T2D consuming (5 ml/day for 12 weeks) *N. sativa* oil.[65] The hypolipidemic and hypoglycemic effects of *N. sativa* oil (1000 mg/day for 8 weeks) were confirmed by Rashidmayvan *et al*. in a randomized, double-blind, placebo-controlled clinical trial performed in patients with nonalcoholic fatty liver.[66] Najmi *et al*. have been reported that the administration of *N. sativa* oil (2.5 mL twice a day for 6 weeks) to patients with metabolic syndrome significantly decreased FBG and LDL and increased HDL levels.[67] Hadi *et al*. in a clinical trial study investigated the effect 1000 mg/days extract of *N. sativa* oil supplementation on 43 patients with T2D. The results after 12-week supplementation of *N. sativa* oil have been shown a significant reduction in serum level of fasting blood sugar, HbA1c, LDL-C, and TG.[68] Table 2 summarizes clinical trials that evaluated the effects of *N. sativa* supplementation on healthy and patient subjects.

## MECHANISMS OF HYPOGLYCEMIC EFFECT OF *NIGELLA SATIVA*

*N. sativa* promotes glucose homeostasis and improves the lipid profile in diabetic animals and humans with T2M through several routes. Mainly, *N. sativa* improve peripheral insulin sensitivity and circulating insulin.[52,53,69] It also enhances the activation of the AMP-activated protein kinase (AMPK) pathway in skeletal muscle and liver and to increased GLUT-4 in skeletal muscle.[70] Acetyl-CoA carboxylase (ACC) is a key component of the insulin-independent, metabolic sensing, and AMPK pathway. In fact, it has been reported that *N. sativa* stimulates ACC and the AMPK pathways in both hepatocyte cell lines and skeletal muscles *in vitro*.[70] Andaloussi *et al*. reported that *in vivo N. sativa* treatment can elevate the phosphorylation of ACC in skeletal muscle tissues and liver. The phosphorylation of ACC decreases its activity and shows a reduction of lipogenesis in the liver, whereas it increases fatty acid oxidation in skeletal muscle. These effects on lipid metabolism can justify the functionality of *N. sativa* to decrease plasma and tissue TG. Finally, it is known that the activation of the AMPK pathway can lead to growing synthesis of GLUT-4[71] [Figure 3]. Many researches suggested that the anti-hyperglycemia and anti-hyperlipidemia features of *N. sativa* are due to antioxidant components.[44,52,67,72,73] TQ and dithymoquinone are the main antioxidant components of *N. sativa.* Several studies have reported that *N. sativa* can enhance antioxidant enzymes and decrease lipid peroxidation.[73] When oxidative stress is reduced, this may help to regeneration of pancreatic beta-cells, increase number of islets, keep the integrity of pancreatic beta-cells, reduction in insulin resistance, increase insulin secretion and inhibition of advanced glycation end product.[59] *N. sativa* oil has been shown to decrease hepatic glucose production from gluconeogenic precursors (alanine, glycerol, and lactate) in STZ-induced diabetic hamster.[74] Furthermore, an *in vitro* study indicated direct inhibition of electrogenic intestinal absorption of glucose by *N. sativa* extract.[32]

## EFFECTS OF *NIGELLA SATIVA* IN RHEUMATOID ARTHRITIS

The anti-RA properties of *N. sativa* and its active ingredient TQ in an animal model were evaluated in experimentally induced arthritis. Findings of a study indicated that treatment with TQ orally (5 mg/kg once daily for 21 days) decreased levels of inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor-α [TNF-α], interferon-gamma [IFN-γ], and prostaglandin E2 [PGE2]) and oxidative stress indices such as articular elastase, myeloperoxidase, lipoxygenase, nitric oxide (NO) significantly and increased levels of anti-inflammatory cytokine IL-10 and the activity of superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT).[75] The results of a study to elucidate the molecular mechanism of the protective effects of TQ showed that the administration of 5 mg/kg TQ orally for 7 days significantly reduced LPS-induced IL-1β, TNF-α, cyclooxygenase-2 (COX-2), metalloproteinase 13 (MMP-13), and PGE2.[76] Some of the studies reported on the effect of *N. sativa* on anti-RA are summarized in Table 1.

### Clinical studies

Clinical trial studies in patients with RA have shown similar results. Hadi *et al*. and Kheirouri *et al*. indicated that two

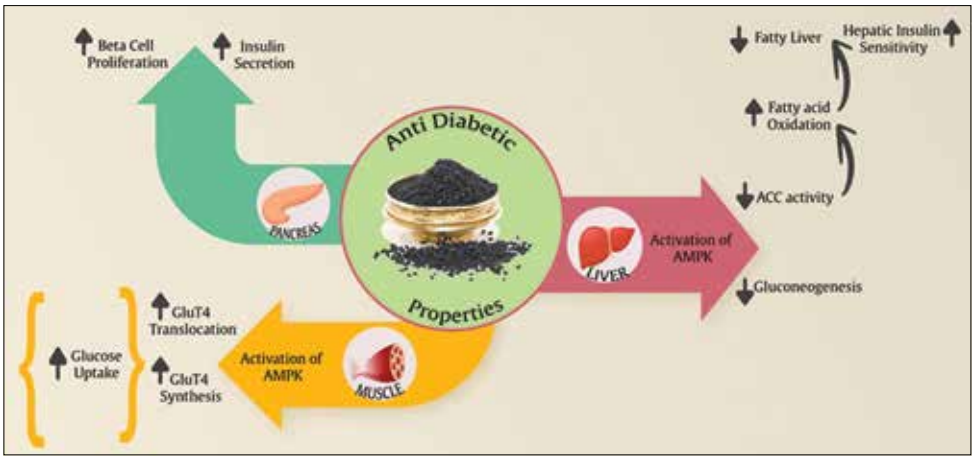


**Figure 3:** Potential mechanisms of the effect of *N. sativa* on diabetes. ACC = Acetyl-CoA carboxylase; AMPK = AMP-activated protein kinase

capsules of 500 mg/day *N. sativa* oil for 8 weeks in patients with RA is significantly reduced in MDA, NO, high-sensitivity C-reactive protein (hs-CRP) level, cytotoxic T-cells (CD8+), Disease Activity Score-28 (DAS-28), and a decreased number of swollen joints in comparison with baseline and placebo groups. Furthermore, *N. sativa* oil is significantly increased in serum level of IL-10, CD4+ T-cell percentage, T regulatory cell percentage (CD4+ CD25+ T-cell), and CD4+/CD8+ ratio. These findings suggest that *N. sativa* by shifting T-helper lymphocyte cells type 1 (Th1) to T-helper lymphocyte cells type 2 (Th2) can improve RA.[77] In another study, the administration of twice capsules 500 mg/day *N. sativa* oil for 4 weeks significantly reduced DAS-28, joint inflammation, and morning stiffness, which could be attributed to the effect of *N. sativa* on the immunomodulatory system.[78] Table 2 summarizes studies investigating the effects of *N. sativa* and its main active ingredient TQ on the anti-RA and anti-inflammatory in clinical studies.

## A MECHANISM OF IMMUNO-MODULATORY PROPERTIES OF *NIGELLA SATIVA*

Several mechanisms for the anti-RA effects of *N. sativa* have been proposed. *N. sativa* with antioxidant, anti-inflammatory, and immunomodulatory properties can be effective.[77] Figure 4 shows the probable mechanisms of the effect of *N. sativa* on RA.

### Antioxidant properties

According to the results of studies, reactive oxygen species (ROS), such as O2, OH, and reactive nitrogen species (RNS) such as NO, play an important role in the enhancement of inflammation and progression of RA.[75,79-81] Therefore, strengthening the antioxidant defense system is very important in reducing chronic diseases.[82] Numerous studies have shown the potentiation of the antioxidant system of *N. sativa*.[34] *N. sativa* exerts its antioxidant properties by direct and indirect antioxidant mechanisms and inhibits the expression of oxidative-producing enzymes (inducible NO synthase [iNOS]). Direct antioxidant activities of *N. sativa* may restore other antioxidants including glutathione (GSH), Vitamin E and Vitamin A, metal chelators, and scavenger free radicals (ROS and RNS). *N. sativa* also exerts its indirect antioxidant role by activating transcription factors involved in the expression of antioxidant enzymes including SOD, glutathione S-transferases (GSTs), GPX, and CAT.[83]

### Anti-inflammatory properties

Inhibition of the nuclear factor-kappa B (NF-κB) pathway is a known mechanism marking anti-inflammatory effects of *N. sativa*.[84] NF-κB is a transcription factor that causes an exacerbation of inflammatory status. This transcription factor is present in the cytosol and has two subunits called P50 and P65. It also binds to the inhibitor of κB (IκBα) inhibitory protein. Factors such as ROS, TNFα, interleukin-1 beta (IL-1B), and bacterial lipopolysaccharides (LPSs) induce NF-κB activity.[85] These factors via activation of IκB kinase (IKK) results in the phosphorylation and destruction of IκBα which results in the activation of NF-κB and its transfer to the nucleus. NF-κB is located in a nucleus on a specific gene sequence that will eventually lead to increased expression of various types of inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, and MMP3), COX-2, and iNOS.[86] These inflammatory cytokines are not only upregulated by NF-κB but also activate NF-κB leading to continuity of inflammatory status.[87] Therefore, *N. sativa* may probably rupture these interactions by NF-κB suppression and plays an important duty in its anti-inflammatory activity.[88] Inhibition of the NF-κB pathway by *N. sativa* can be done in several ways: (1) preventing NF-κB transfer from the cytosol to the nucleus, (2) blocking the NF-KB subunit P50 bonded to the promoter of genes expressing inflammatory factors, especially TNF-α, (3) inhibition of NF-κB p65 subunit nuclear expression, and (4) prevention of phosphorylation and degradation of I-KBα (binding of

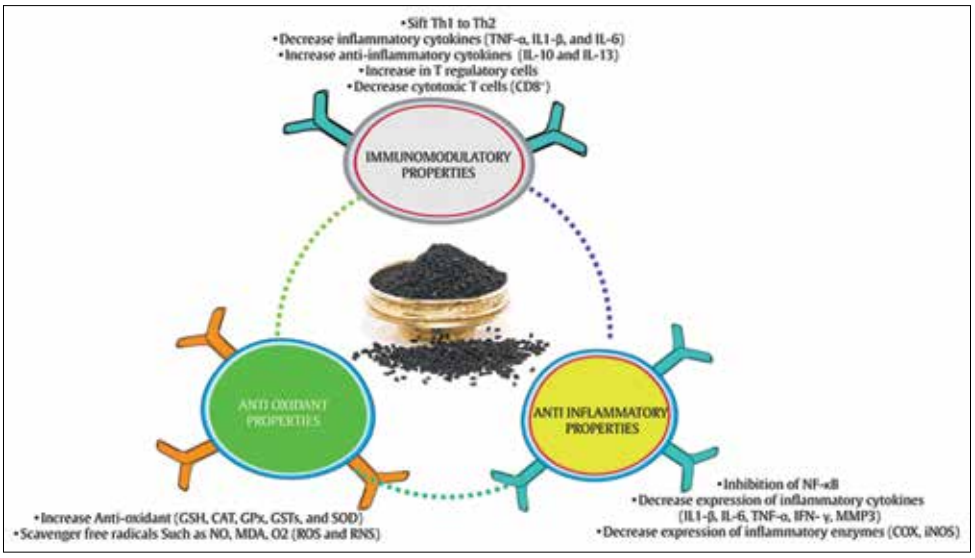


**Figure 4:** Probable mechanisms of the effect of *N. sativa* on rheumatoid arthritis. NF-κB = Inhibition of the nuclear factor-kappa B; TNF-α = Tumor necrosis factor-alpha; IL-1β = Interleukin-1β; IL-6 = Interleukin-6; IFN-γ = Interferon-gamma; MMP-3 = Matrix metalloproteinase 3; COX = Cyclooxygenase; iNOS = Inducible nitric oxide synthase; GSH = Glutathione; CAT = Catalase; *GPX* = Glutathione peroxidase; GSTs = Glutathione S-transferases; SOD = Superoxide dismutase; NO = Nitric oxide; MDA = Malondialdehyde; ROS = Reactive oxygen species; RNS = Reactive nitrogen species; Th1 = Type 1 helper T-cells; Th2 = Type 2 helper T-cells; IL-10 = Interleukin-10; IL-13 = Interleukin-13

I-KBα to NF-κB causes inactivation of this transcription factor).[87]

### Immunomodulatory properties

Studies suggest that *N. sativa* can regulate immune responses.[82] In RA, decreased expression of IL-10 produced by Th2 can be accountable for the dominance of T-helper 1 over T-helper 2 cells at sites of inflamed synovium and in the peripheral blood and reduce in Th2 may exacerbate the inflammatory process in RA. *N. sativa* probably shifts the immune response from Th1 that produces pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 to Th2 that results in anti-inflammatory cytokines such as IL-10 and IL-3. Studies have shown that an increase in IL-10 and IL-3 leads to an increase in T regulatory cell percentage (CD4+CD25+T-cell).[89-91] T regulatory cells reduce the abnormal proliferation of immune cells, such as cytotoxic T-cells (CD8+) and Th1 cells, which is responsible for the secretion of many inflammatory cytokines.[91-93] Therefore, *N.sativa* by regulation of T-lymphocytes leading to improve clinical symptoms of RA.[91]

## CONCLUSION

This review article demonstrated that *N. sativa* could reduce oxidative stress and inflammation with various mechanisms have been proposed to contribute to the beneficial properties of N. *sativa*, including a reduction of lipid peroxidation via its antioxidant properties; agonist of PPAR-γ in adipose tissue; activation of AMPK, increased antioxidants inhibition of NF-κB pathway; increased in IL-10 expression, CD4+ T-cell percentage, T regulatory cell percentage in peripheral blood, and CD4+/CD8+ ratio. Therefore, *N. sativa* may be beneficial in chronic diseases (CVD, T2D, and RA) and can be used as an adjunct therapy. Furthermore, clinical studies have shown a positive effect of *N. sativa* on BP, FBG, and lipid profile, but to prove this claim, it is necessary to conduct experimental and well-designed clinical trial studies with a larger sample size on the effects of *N. sativa* on these chronic diseases.

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### Conflicts of interest

There are no conflicts of interest.

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