Review Article

Cardiovascular Effects of *Nigella Sativa* L. and its Constituents

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Shakeri, *et al.*: Cardiovascular effects of *Nigella sativa*

Various pharmacological effects of *Nigella sativa* L. have been reported that include, antioxidant, antibacterial, antihistaminic, antihypertensive, hypoglycemic, antifungal, antiinflammatory, anticancer, and immunomodulatory. It has also been reported to produce beneficial effects in cardiovascular, gastrointestinal, reproductive and respiratory disorders. The effects of *Nigella sativa* had been attributed to constituents such as nigellicine, nigellidine, thymoquinone, dithymoquinone, thymol and carvacrol. In this article the cardiovascular effects of *Nigella sativa* and its constituents were reviewed. Published data was gathered through search engines and the findings were classified into animal and human studies. The effects of *Nigella sativa* and its constituents on cardiotoxicity, blood pressure, vascular smooth muscle, endothelial dysfunction, heart rate, cardiac contractility, lipid profile, platelet aggregation and atherosclerosis were reviewed. This review indicated that *Nigella sativa* and thymoquinone exhibited beneficial cardiovascular effects on cardiotoxicity, hypertension, hyperlipidemia, and atherosclerosis. These effects were probably due to the antioxidant and antiinflammatory properties of *Nigella sativa*. *Nigella sativa* and its constituents could be of therapeutic value in cardiovascular diseases.

Key words: Thymoquinone, cardiovascular disease, hypertension, atherosclerosis, hyperlipidemia

Nigella sativa L. (Ranunculaceae) is an annual flowering plant with green-to-blue-colored flowers and black seeds, native to southwest Asia, southern Europe and North Africa but it is cultivated and used in other parts of the world[1].

Crude oil derived from the seeds of *N. sativa* exhibited a variety of pharmacological effects such as antihistaminic[2,3], anticholinergic[4], diuretic and antihypertensive[5,6], hypoglycemic[7], antioxytocic[8], antinociceptive[9], respiratory stimulator[10], antiasthma and antidyspnea[11], antitussive[12], bronchodilatory[13], tracheal smooth muscle relaxant[14,15], hematological[16], hepatoprotective[17], immunopotentiating[18], anticancer[19], antimicrobial, antiinflammatory[20,21], antifungal[22], antiulcer[23] and antioxidant[24]. *N. sativa* seed oil is also effective in treating headache, flatulence, blood homeostasis abnormalities, rheumatism and related inflammatory diseases[25]. Chemical composition of *N. sativa* seed extracts analysed by supercritical CO_2 extraction included *n*-nonane, tricyclene, camphene, *β*-pinene, *β*-myrcene, 1,8-cineole, *α*-terpinene, limonene, linalool, terpinolene, borneol, pinocarvone, thymoquinone (TQ), thymol, carvacrol, cyclosativene, α-longicyclene, palmitic acid, octadecanoic acid, dihydrofarnesyl acetate, davanone and dihydrofarnesyl acetate[26]. Pharmacological properties of *N. sativa* could be attributed to the constituents like nigellicine, nigellidine, TQ, dithymoquinone, thymol, and carvacrol[27] (fig. 1). Alimohammadi *et al*. reported that the extract of *N. sativa* reduced blood glucose due to inhibition of hepatic gluconeogenesis and possible insulin tropic properties[28]. Treatment with *N. sativa* markedly decreased the fasting blood glucose (FBG) level in streptozotocin (STZ) diabetic rats. Histopathological examination also indicated that the *N. sativa* partially ameliorated hepatic glycogen content and preserved the pancreatic islet cells[28]. In addition, extracts of *N. sativa* and its constituents

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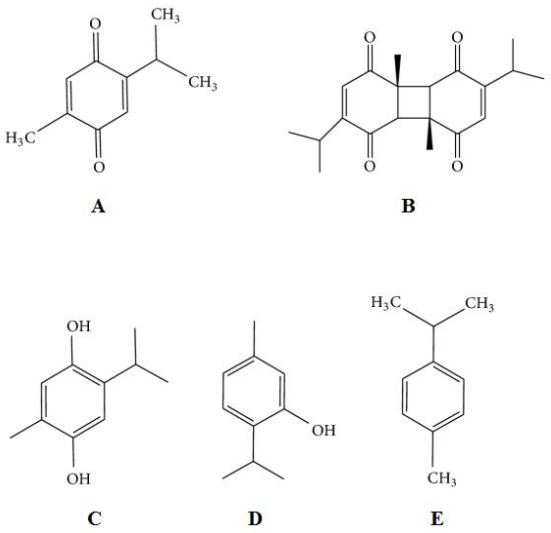

Fig. 1: Chemical structure of some potentially bioactive compounds in *N. sativa*
A: Thymoquinone; B: dithymoquinone; C: thymohydroquinone; D: thymol; E: *p*-cymene

could lower blood pressure through blockade of calcium channels[29,30]. The plant also showed a potent inhibitory effect on both heart rate and contractility of isolated guinea pig heart comparable and even higher than that of diltiazem[31,32]. In the present review, the cardiovascular effects of *N. sativa* and its constituents were presented.

Online literature searches were performed using Medline, PubMed, Science Direct, Scopus, and Google Scholar websites from 1965 to 2015 to identify studies about cardiovascular effects of *N. sativa* and its constituents. The keywords used were; *N. sativa*, cardiovascular, cardiotoxicity, blood pressure, vascular smooth muscle, endothelial dysfunction, heart rate, heart contractility, lipid profile, platelet aggregation, and atherosclerosis. The search results were checked by two authors and cited articles were reviewed by authors. Therefore, the risk of bias within the studies and across the studies as far as this review concern was avoided. There was no obvious limitation at the review level. However, only few studies were found regarding the clinical effect of the plant and its constituents on cardiovascular diseases. Therefore, only limited information at the outcome level could be presented in this review.

LABORATORY ANIMAL STUDIES

Effect on cardiotoxicity:

Treatment with *N. sativa* seed powder (4 % w/w) and/or aqueous solution of bees' honey (2.5 g/kg/day) showed a protective effect on the heart disorder induced by food additives in rats[33]. Cardioprotective effect of *N. sativa* seed oil administered 4 ml/kg orally, 1 h before the administration of lead acetate 20 mg/kg, intraperitoneal (ip) 3 d weekly for 8 w on lead-induced cardiotoxicity in rats has been reported. Findings showed that *N. sativa* seed oil decreased heart rate, changes in ST segment, which is the isoelectric section of the ECG between the end of the S wave and the beginning of the T wave also known as the J point, proinflammatory cytokine levels, oxidative stress and cardiac tissue damage[34]. Pretreatment with *N. sativa* oil (2 ml/kg, per oral, po) in cyclosporine A-induced cardiomyopathy (25 mg/kg po) in rats for three weeks decreased the cyclosporine A injury in the heart and lipid peroxidation, normalized cardiac histopathology, improved antioxidant enzyme status and cellular protein oxidation[35]. Pretreatment with TQ (100 mg/kg, po) and *N. sativa* seed oil (100 µl/kg) reduced the plasma levels of triglycerides, lipid peroxidation, cholesterol, glutathione peroxidase and superoxide dismutase (SOD) activities on methionine-induced hyperhomocysteinemia in rats[36].

The cardioprotective effect of TQ (50 mg/l in drinking water), the main constituent of the volatile oil of *N. sativa* seed, on cyclophosphamide-induced cardiotoxicity in albino rats was evaluated by Nagi *et al*. in 2011[37]. Findings showed that treatment with TQ caused a complete reversal of all the biochemical changes induced by cyclophosphamide and decreased oxidative and nitrosative stress as well as improved antioxidant enzyme status, mitochondrial function and energy production in heart tissues. The effect of TQ (8-10 mg/kg/day, po) on doxorubicin-induced cardiotoxicity (15-20 mg/kg as a single ip injection) was also demonstrated that TQ when given in the drinking water protects rats from doxorubicin-induced cardiotoxicity as evidenced by significant reductions in serum lactate dehydrogenase and creatine kinase. The superoxide scavenging, antilipid peroxidation and cytoprotective agent may explain such effect[38,39]. The protective effect of TQ (5, 10 and 20 mg/kg/day) on cypermethrin-induced (10 mg/kg/day, po) necrosis, degeneration, and loss of striation in heart for 28 d in albino mice showed that treatment with TQ caused reversal of all biochemical changes induced by cypermethrin and decreased oxidative stress lipid peroxidation[40].

The protective effect of TQ on the acute (at 4 and 18 h) effects of diesel exhaust particles (DEP, 30 mg/mouse, intratracheal) on cardiopulmonary parameters in mice also showed that pretreatment of

mice with TQ (6 mg/kg; ip), 24 and 1 h before DEP, decreased IL-6 concentration, leukocytosis, airway hyperresponsiveness to methacholine and increased systolic blood pressure (SBP), platelet numbers, plasma SOD activity[41]. The effect of TQ (12.5, 25 and 50 mg/kg, po) on isoproterenol-induced myocardial injury in rats showed that TQ decreased plasma SOD activity, myocardial glutathione (GSH)/glutathione disulphide ratio and histological changes induced by isoproterenol[42]. The effects of *N. sativa* and its constituents on cardiotoxicity were summarized in Table 1.

Effect on blood pressure:

The diuretic and hypotensive effects of dichloromethane extract of *N. sativa* in the spontaneously hypertensive rat indicated that oral administrations of *N. sativa* extract (0.6 ml/kg/day) and furosemide (5 mg/kg/day) significantly increased the diuresis by 16 and 30 %, respectively after 15 d of treatment and reduced the mean arterial pressure (MAP) by 22 and 18 %, respectively[6]. The protective effect of *N. sativa* (0.2 ml/kg/day, ip) against oxidative injury in the heart and kidney tissues of rats with renovascular hypertension model induced by placing a renal artery clip was investigated. The findings showed that *N. sativa* significantly reduced blood pressure, attenuated oxidative injury and improved left ventricular function. The results also suggested that *N. sativa* protected against hypertension-induced tissue damage and improved cardiovascular function by its antioxidant and antihypertensive effects[43]. The effect of *N. sativa* on L-NAME-induced hypertensive rats also showed that oral administration of *N. sativa* (2.5 ml/kg/day) reduced SBP and diastolic blood pressure (DBP). The results also suggested that this effect of *N. sativa* may be mediated by stimulating nitric oxide release from vascular endothelium[44].

The volatile oil of the *N. sativa* seed (4-32 µl/kg, intravenous, iv) reduced arterial blood pressure and heart rate in a dose-dependent manner in guinea-pigs[45]. The effect of aqueous extract of *N. sativa* on spontaneously hypertensive rats was also showed that *N. sativa* significantly reduced SBP and increased urinary output and glomerular filtration rate. These results also suggested that the antihypertensive effect of *N. sativa* is mediated by increasing urinary and electrolyte output[46]. The effects of *N. sativa* seeds and *Syzygium aromaticum* extracts on L-NAME-induced hypertensive rats showed that *N. sativa* (400 mg/kg) and *S. aromaticum* (100 mg/kg) reduced SBP, DBP, MAP, LDL and increased serum nitric oxide level[47]. The effect of volatile oil of the *N. sativa* seed and TQ on the arterial blood pressure and heart of urethane-anaesthetized rats showed that treatment with volatile oil of *N. sativa* seed (4-32 µl/kg, iv) or TQ (0.2-1.6 mg/kg, iv) decreased the arterial blood pressure and the heart rate in a dose-dependent manner[5]. The protective effect of TQ (0.5 and 1 mg/kg/day, po), on L-NAME-induced hypertension (50 mg/kg/day, po) for 4 w in rats was evaluated by Khattab *et al*. in 2007 and the findings showed that TQ reduced the increase in SBP induced by L-NAME in a dose-dependent manner and decreased the elevated creatinine and increased GSH to normal levels[48]. The hypotensive effect of α-pinene (1, 5, 10, and 20 mg/kg, iv), a constituent of the essential oil of *N. sativa* seed was seen in non-anaesthetized normotensive rats[49]. Dethymoquinonated volatile of *N. sativa* seed, α-pinene and p-cymene also in a dose range (2-16 µl/kg, iv) reduced blood pressure and heart rate in urethane-anaesthetized rats, which is mediated by inhibition of vasomotor center[50]. The effects of *N. sativa* and its constituents on blood pressure are summarized in Table 1.

Effect on vascular smooth muscle and endothelial dysfunction:

The essential oil from the seeds of *N. sativa* exhibited a depressant effect on the frog heart and a relaxant property on isolated vascular smooth muscles of rat[51]. The vasorelaxation effect of cumulative concentration of the hydro-ethanolic extract of *N. sativa* (2, 4, 6, 8, 10, and 14 mg/ml) on rat aortic smooth muscle contracted by both KCl and phenylephrine was shown[52]. In the other study by Suddek in 2010[53], the effect of TQ on smooth muscle of pulmonary artery was investigated. TQ caused a concentration-dependent decrease in the tension of the pulmonary arterial smooth muscles precontracted by phenylephrine. Furthermore, the relaxant effect of *N. sativa* may be mediated by the activation of ATP-sensitive potassium channels and probably by non-competitive blocking of serotonin, alpha1 and endothelin receptors[53].

Endothelial dysfunction with ageing is due to the endothelial release of vasoconstrictor prostaglandins and imbalance between the production of NO and endothelium-derived hyperpolarizing factor. The oral administration of TQ (10 mg/kg/day) improved endothelial function by inhibition of oxidative stress and normalization of the angiotensin system in rat

TABLE 1: THE EFFECT OF *N. SATIVA* AND ITS CONSTITUENTS ON CARDIOTOXICITY AND BLOOD PRESSURE

Plant preparation	Study model	Effect	Reference
N. sativa and honey	Sodium nitrite and sunset yellow-induced heart disorder	Modulating heart disorder induced by food additives	[33]
N. sativa oil	Lead-induced cardiotoxicity in rat	Decreased heart rate, ST segment change, pro inflammatory cytokines, oxidative stress and cardiac tissue damage	[34]
N. sativa oil	Cyclosporine A-induced cardiomyopathy in rat	Normalized cardiac histopathology, decreased lipid peroxidation, improved antioxidant enzyme status and cellular protein oxidation	[35]
N. sativa oil and TQ	Methionine-induced hyperhomocysteinemia in rat	Decreased TG, lipid peroxidation and TC	[36]
TQ	Cyclophosphamide-induced cardiotoxicity in rat	Decreased oxidative and nitrosative stress, improved antioxidant enzyme status and mitochondrial function in heart tissues	[37]
TQ	Doxorubicin-induced cardiotoxicity in rat	Reduced serum lactate dehydrogenase and creatine kinase	[38-39]
TQ	Cypermethrin-induced cardio toxicity in rat	Decreased oxidative stress and lipid peroxidation	[40]
TQ	Diesel exhaust particles-induced cardiotoxicity in rat	Decreased of SBP, leucocytosis, platelet counts and the prothrombotic activity, increased IL-6 concentration and decreased plasma SOD activity	[41]
TQ	Isoproterenol-induced myocardial injury in rats	Decreased plasma SOD activity, myocardial GSH/GSSG ratio and histological changes	[42]
N. sativa	RVH model in rat	Reduced BP, oxidative injury, improved left ventricular function	[43]
N. sativa	L-NAME-induced hypertension in rat	Reduced SBP and DBP	[44]
N. sativa and *S. aromaticum* extract	L-NAME-induced hypertension in rat	Reduced SBP, DBP, MAP, LDL, increased serum nitric oxide	[47]
Aqueous extract	Spontaneously hypertensive rat	Reduced SBP Increased urinary output and glomerular filtration rate	[46]
Dichloromethane extract	Spontaneously hypertensive rat	Increased the diuresis, reduced MAP	[6]
Volatile oil	Normotensive guinea pigs	Reduced BP and heart rate in a dose dependent manner	[45]
Volatile oil and TQ	Urethane-anaesthetized rat	Decreased arterial blood pressure and heart rate in a dose-dependent manner	[5]
Alpha-pinene	Non-anaesthetized normotensive rat	Hypotensive effect	[49]
Dethymoquinonated volatile of *N. sativa*, α-pinene and p-cymene	Urethane-anaesthetized rat	Reduced BP and heart rate	[50]
TQ	L-NAME-induced hypertension in rat	Reduced SBP in a dose dependent manner, decreased creatinine and increased GSH to normal levels	[48]

SOD: superoxide dismutase, TG: triglyceride, TC: total cholesterol, GSH/GSSG: glutathione/oxidized glutathione, SBP: systolic blood pressure, RVH: renovascular hypertension, L-NAME: L-NG-nitroarginine methyl ester, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, LDL: low-density lipoprotein, TQ: thymoquinone, GSH: glutathione

mesenteric artery[54]. The effects of *N. sativa* and its constituents on vascular smooth muscle and endothelial dysfunction were summarized in Table 2.

Effect on heart rate and heart contractility:

The effects of aqueous and macerated extracts from *N. sativa* (0.5, 1.0, 2.0 and 5.0 mg, %) on heart rate and contractility of isolated heart in guinea pig showed a potent inhibitory effect of both extracts from *N. sativa* on heart rate and contractility, which was comparable and even higher than that of diltiazem. It is suggested that two probable mechanisms for these effects are calcium channel blocking and an opening effect of the plant on potassium channels of the isolated heart[31,32]. The effect of oral administration of *N. sativa* (800 mg/kg) on intrinsic cardiac responses showed that *N. sativa*

TABLE 2: THE EFFECT OF *N. SATIVA* AND ITS CONSTITUENTS ON VASCULAR SMOOTH MUSCLE, ENDOTHELIAL DYSFUNCTION, HEART RATE AND HEART CONTRACTILITY

Plant preparation	Study model	Effect	Reference
Essential oil of *N. sativa*	Isolated vascular smooth muscles of rat	Depressant effect on the frog heart and a relaxant property	[51]
Hydroethanolic extract	Rat aortic smooth muscle contracted by both KCl and phenylephrine	The vasorelaxation effect	[52]
TQ	Smooth muscle of pulmonary artery contracted by phenylephrine	The relaxant effect	[53]
TQ	Endothelial dysfunction with ageing in rat mesenteric artery	Improved endothelial function by inhibition of oxidative stress and normalization angiotensin system	[54]
N. sativa	The intrinsic cardiac responses	Increased left ventricular and whole heart weights, improved baseline peak tension heart rate and myocardial flow rate	[55]
N. sativa	Cardiac reserve in rats	Increase heart weight to body weight ratio and baseline cardiac inotropic properties	[57]
N. sativa	*N. sativa* supplementation and exercise training in rat	Cardiac hypertrophy, reduced heart rate	[58-59]
N. sativa	Myocardial ischemic reperfusion injury in rat	Increased contractile and vascular functions, reduced oxidative stress in cardiac tissue	[60]
N. sativa	Cadmium-treated rats	Decreased heart rate, glucose concentration, increased RBC, WBC counts, Hb, and PCV.	[61]
N. sativa	Alloxan-induced diabetic rabbits	Reduced heart rate	[62]
N. sativa seed and oil extract	Isoproterenol-induced myocardial infarction in rats	Normalized altered levels of LDH, CPK, AST, ALT and lipid profile	[63]
Aqueous and macerated extracts of *N. sativa*	Isolated heart in guinea pig	Inhibitory effect on heart rate and heart contractility	[31-32]

RBC: red blood cell, WBC: white blood cell, Hb: hemoglobin, PCV: packed cell volume, LDH: lactate dehydrogenase, CPK: creatine phosphokinase,, AST: aspartate aminotransferase, ALT: alanine aminotransferase

significantly increased left ventricular and whole heart weights and enhanced levels of baseline peak tension, maximum rate of tension development, heart rate and myocardial flow rate[55]. The effect of oral administration of *N. sativa* (800 mg/kg) for two months on cardiac hemodynamics and adrenergic responsiveness also showed that *N. sativa* resulted on intrinsic cardiac contractile properties without evidence of increased cardiac work load or energy consumption *in vivo*[56]. Furthermore, the supplementation of *N. sativa* for one month on cardiac reserve in rats showed that *N. sativa* developed a moderate but significant hypertrophy that was evident by an increase in the heart weight to body weight ratio and associated with an increase in the baseline cardiac inotropic properties[57].

Combination of *N. sativa* supplementation and exercise training might induce a safer model of cardiac hypertrophy. The effects of *N. sativa* (800 mg/kg) and exercise (on treadmill, 2 h/day) on cardiac hypertrophy in rats showed a synergistic effect of *N. sativa* treatment with exercise training as *N. sativa*-exercise-induced cardiac hypertrophy had lower heart rate and well-matched electrical activity of the heart to its mass[58,59]. In a model of myocardial ischemic reperfusion injury in rats, it was shown that oral administration of *N. sativa* (800 mg/kg) increased contractile and vascular functions and reduced oxidative stress in the cardiac tissue. It also protected the heart against mitochondrial permeability transition pore opening[60]. The effect of *N. sativa* (2 ml/kg, ip) on the heart rate, some haematological values, and pancreatic β-cell damage in cadmium-treated rats was showed that *N. sativa* decreased the elevated heart rate, glucose concentration and increased the lowered RBC and WBC counts as well as hemoglobin (Hb) and packed cell volume values. The results also suggest that the preventive effects of *N. sativa* may be mediated by the inhibition of lipid peroxidation and antioxidant property[61]. Furthermore, the effect of the plant (20 ml/kg) on heart rate in alloxan-induced diabetic rabbits showed that *N. sativa* treatment decreased the diabetes-induced disturbances of heart rate and some haematological parameters of alloxan-induced diabetic rabbits[62]. In isoproterenol-induced myocardial infarction, *N. sativa* seed extract

(1000 mg/kg, po) and oil extract (2 ml/kg, po) treatment for 21 d resulted in normalized levels of LDH, CPK, AST, ALT, lipid profile[63]. The effects of *N. sativa* and its constituents on heart rate and heart contractility were summarized in Table 2.

Effect on lipid profile:

The effect of methanolic extract (810 mg/kg) and volatile oil (410 mg/kg) of *N. sativa* seed on hyperlipidaemia rat showed that treatment with the plant significantly reduced the levels of plasma triglycerides (TG), total cholesterol (TC), very low density lipoproteins (VLDL-C), low density lipoproteins (LDL-C), β-hydroxy β-methylglutaryl-CoA reductase activity and increased high density lipoproteins (HDL-C) concentration[64]. Intra-gastric gavage of petroleum ether extract of *N. sativa* seeds reduced fasting plasma levels of insulin and TG and increased HDL-C[65]. Furthermore, oral administration of *N. sativa* seed fixed oil (1 ml/kg) in rats for 12 w reduced TC, TG, glucose levels as well as leukocytes and platelets counts and increased hematocrit and Hb levels[60-66]. Treatment with *N. sativa* seed oil (800 mg/kg, p.o. for 4 w) in rats was also significantly decreased serum TC, LDL, TG and increased serum HDL[61-67]. Treatment with *N. sativa* (50, 100, 200, 300, 400, 500 mg/day) also reduced serum TC, LDL, TG and increased HDL/LDL ratio in normal rats[68]. The inhibitory effects of ethanolic extract of *N. sativa* seed (0.5, 1 and 1.5 mg/kg, ip) on adrenaline-induced dyslipidaemia and left ventricular hypertrophy in rats was showed that injection of the plant on adrenaline-induced dyslipidaemia rats for two weeks significantly reduced TC, TG, LDL-C and increased HDL-C. However, treatment with *N. sativa* for eight weeks increased free radical scavenging activity and decreased the left ventricular hypertrophy and cardiomyocyte size[69].

N. sativa (1000 mg/kg/day) in comparison to simvastatin, a synthetic antihyperlipidemic drug in Sprague Dawley rats showed significant reduction in TC, TG, LDL-C and increase of HDL-C. The results suggested that *N. sativa* could be used as an antihyperlipidemic drug without any side-effects[70,71]. Significantly reduction of TC, TG, LDL-C, and MDA has also been demonstrated as the effect of *N. sativa* seed crushed treatment (7.5 g/kg/day) in a rabbit model of hyperlipidemia[72]. Furthermore, treatment with *N. sativa* (5 %) significantly reduced TC and LDL-C in hypercholesterolemia rabbits[73,74].

The effect of different extracts of *N. sativa* on lipid profile in ovariectomized rats as an animal model of menopause was evaluated and the results showed that different extracts of *N. sativa* significantly reduced blood glucose and LDL-C, although the differences in TC, TG and HDL-C were not significant[75]. Treatment of either *N. sativa* (0.4 mg/kg) or olive oil (0.4 mg/kg) in a mice model of hyperlipidaemia significantly reduced TC, TG, LDL-C and VLDL-C. However, the value of HDL-C in olive oil group was significantly higher than in *N. sativa* group[76]. The effect of acetone extracts of *N. sativa* (0, 0.2, 0.4 % and *N. sativa* seed powder (0, 1.5, 2.5, 3.0 %) on hyperlipidaemia broiler chicks for 4 w showed that supplementation of either the seed powder or acetone extracts of the plant seeds significantly reduced TC and TG[77]. The results of the effect of *N. sativa* seed oil on lipid profile in sheep in contrast to previous findings showed that feeding with 4.7 % of the plant oil in diets of sheep significantly increased TC, TG, LDL-C, and HDL-C[78]. Supplementation of *N. sativa* seed (2 %) also reduced HDL-C and elevated TC, TG, LDL-C, VLDL-C in Pekin ducklings[79].

Canola oil and *N. sativa* seed powder significantly reduced TC and LDL-C but non-significantly increased HDL-C[80]. Furthermore, treatment with *N. sativa* (30 mg/kg, po) significantly increased HDL-C and decreased LDL-C[81]. Palm oil increased the TC and LDL-C; decreased HDL-C levels in albino rats at 24 w but treatment with *N. sativa* significantly reduced TC and LDL-C and increased HDL-C levels[82,83]. Supplementation with 5 % *N. sativa* significantly decreased arterial wall lipid deposition, TC and LDL in hypercholesterolemia rabbits[73]. TQ (10 mg/kg, po) reduced TC, TG, and LDL-C and increased HDL-C for a period of eight weeks in a rabbit model of atherosclerosis although the differences in lipid profile were not significant[84,85]. Table 3 presented the effects of *N. sativa* and its constituents on lipid profile.

Antiatherogenic and antiplatelet effects:

The effect of *N. sativa* seeds powder (1000 mg/kg) and oil (500 mg/kg) in comparison to simvastatin (10 mg/kg) on atherosclerosis in diet-induced hypercholesterolemia rabbits for a period of eight weeks was investigated and the results indicated that treatment with *N. sativa* either powder or oil significantly reduced arterial wall lipid deposition, TC and LDL and increased HDL. In addition, plaque formation significantly inhibited and reduced the intima/media ratio[86]. The *N. sativa* seeds powder (100 mg/kg/day) in diet-induced

TABLE 3: THE EFFECT OF *N. SATIVA* AND ITS CONSTITUENTS ON LIPID PROFILE

Plant preparation	Study model	Effect	Reference
N. sativa	Rat	Increased HDL-C, decreased LDL-C	[81]
N. sativa	Rat feeded with palm oil	Reduced TC and LDL-C, increased HDL-C	[82,83]
N. sativa	Rat feeded with cholesterol rich diet	Reduced TC, TG, LDL-C, increased HDL-C	[70,71]
N. sativa	Hyperlipidemia rabbit	Reduced TC, TG, LDL-C, MDA	[72]
N. sativa	Hypercholesterolemia rabbit	Reduced TC and LDL-C	[73]
N. sativa	Sunflower oil, cholic acid and propylthiouracil diet in rat	Reduced TC, TG, LDL-C, increased HDL-C	[74]
N. sativa	Rat	Reduced TC, LDL, TG, increased HDL/LDL ratio	[68]
N. sativa and olive oil	Hyperlipidemia mice	Reduced TC, TG, LDL-C and VLDL-C, increased HDL-C	[76]
N. sativa seed	Pekin ducklings	Reduced HDL-C, elevated TC, TG, LDL-C, VLDL-C	[79]
N. sativa seed powder and Canola oil	Rat	Reduced TC and LDL-C	[80]
N. sativa seed fixed oil	Rat	Reduced TC, TG, glucose levels, leukocytes and platelets counts, increased hematocrit and hemoglobin levels	[66]
N. sativa oil	Sheep	Increased TC, TG, LDL-C, HDL-C	[78]
N. sativa oil	Rat	Decrease TC, LDL, TG, increased HDL	[67]
Methanolic extract and volatile oil of *N. sativa*	Hyperlipidemia rat	Reduced TG, TC, VLDL-C, LDL-C, HMG-CoA reductase activity, increased HDL-c	[64]
Petroleum ether extract of *N. sativa* seeds	Rat	Reduced fasting plasma levels of insulin and TG, increased HDL-C	[65]
Ethanolic extract of *N. sativa* seed	Adrenaline-induced dyslipidemia and left ventricular hypertrophy in rats	Reduced TC, TG , LDL-C, increased HDL-C	[69]
Supercritical fluid, methanol and hexane extract of *N. sativa*	An animal model of menopause	Reduced blood glucose and LDL-C	[75]
Acetone extract and *N. sativa* seed powder	Hyperlipidemia broiler chicks	Reduced TC and TG	[77]

TG: triglyceride, TC: total cholesterol, VLDL-C: very low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, MDA: malondialdehyde

hypercholesterolemia rabbits for a period of four weeks was significantly reduced serum levels of TC, TG, and LDL-C and increased HDL-C[87]. The methanol soluble portion of the *N. sativa* seed oil showed inhibitory effects on arachidonic acid (AA)-induced platelet aggregation and blood coagulation. Some isolated compounds from the oil such as 2-(2-methoxypropyl)-5-methyl-1,4-benzenediol, thymol, carvacrol showed significantly higher effect on AA-induced platelet aggregation and blood coagulation than aspirin[16]. In addition, fatty streak formation significantly reduced in the left and right coronary arteries and the aorta. The results suggested that this effect of *N. sativa* may be related to its antioxidant and antiinflammatory properties[88,89]. Treatment with propolis (a resinous hive product collected by honeybees from various plant sources) and TQ in hypercholesterolemia rabbits also showed significant reduction of serum TC, LDL-C, triglycerides and thiobarbituric acid-reactive concentrations, and increased HDL-C concentration, as well as glutathione content. Histopathological examination showed protective effect of propolis and TQ against hypercholesterolemia-induced aortic tissue damage. The results also suggested that the protective effects of propolis and TQ maybe mediated by antioxidant mechanism[90]. Antiatherogenic and antiplatelet effects of *N. sativa* and its constituents have been shown in Table 4.

CLINICAL STUDIES

Effect on blood pressure:

Oral treatment of *N. sativa* seed in male patients with mild hyperlipidaemia and hypertension for a period of 8 w demonstrated a significant dose-dependent decline in the levels of SBP and DBP[91]. The antihypertensive effect of *N. sativa* seed oil was evaluated on patients with metabolic syndrome divided in two groups of one, triple therapy including amlodipine 5 mg, atenolol

TABLE 4: ANTIATHEROGENIC, ANTIPLATELET AND BLOOD PRESSURE-LOWERING EFFECTS OF *N. SATIVA* AND ITS CONSTITUENTS

Plant preparation	Study model	Effect	Reference
N. sativa	Hypercholesterolemia rabbit	Decreased TC, LDL-C and fatty streak formation	[88,89]
N. sativa seeds powder	Hypercholesterolemia rabbit	Reduced TC, TG, LDL-C, increased HDL-C	[87]
N. sativa seeds powder and oil	Hypercholesterolemia rabbit	Reduced arterial wall lipid deposition, TC, LDL, plaque formation and the intima: media ratio, increased HDL	[86]
Methanol soluble portion of the *N. sativa* seed oil	Arachidonic acid (AA)-induced platelet aggregation and blood coagulation	Inhibitory effect on platelet aggregation and blood coagulation	[16]
TQ and propolis	Hypercholesterolemia rabbit	Reduced TC, LDL-C, TG and thiobarbituric acid-reactive substances, increased HDL-C and glutathione content	[90]
N. sativa seed	Patients with mild hyperlipidemia and hypertension	Dose-dependent decline in SBP and DBP	[91]
N. sativa oil	Patients with metabolic syndrome	Decreased SBP, DBP	[92]
N. sativa oil	Normal healthy human	Decreased SBP and DBP	[93]
N. sativa seeds and honey mixture	Hypercholesterolemia patients	Decreased SBP, DBP	[94]

TG: triglyceride, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, TQ: thymoquinone, SBP: systolic blood pressure, DBP: diastolic blood pressure

50 mg and atorvastatin 10 mg once a day and the second, triple therapy+a capsule containing 500 mg *N. sativa* extract. Aspirin 150 mg was given in both groups for a period of eight weeks. The findings of this study showed that *N. sativa* significantly decreased SBP, DBP and LDL-C and increased HDL. These findings suggest that *N. sativa* has significant hypertensive property and effect on dyslipidaemia. These results also suggested that two possible mechanisms responsible for antihypertensive effects of *N. sativa* are calcium channel blocking and diuretic activity[92]. The effect of *N. sativa* seed oil on SBP and DBP in healthy volunteers was also investigated. Each subject in the *N. sativa* seed oil group received a bottle containing 150 ml *N. sativa* seed oil and in the placebo group received a bottle containing 150 ml mineral oil every 4 w during the 8 w trial. The results indicated that *N. sativa* significantly decreased SBP and DBP[93]. Combination therapy of *N. sativa* seeds (50 mg/kg b.w) and honey mixture also significantly reduced SBP and DBP[94]. The clinical effects of *N. sativa* and its constituents on blood pressure are summarized in Table 4.

Effect on lipid profile:

In a clinical study, the effects of *N. sativa* seed powder on serum cholesterol, HDL and LDL-c and TG in menopausal women of 2 groups including: treatment group received *N. sativa* powder (500 mg) capsules and placebo group received the placebo capsules (wheat germ, 100 mg) was investigated. Capsules of *N. sativa* powder were orally administered at a dose of 1 g after breakfast every day for a period of two months. The results indicated that *N. sativa* significantly increased serum HDL-C and decreased LDL-C, TC, TG and FBG. However, the differences in BP were not significant between the treatment and placebo over the period of intervention[95]. Treatment with *N. sativa* seed oil also significantly increased serum HDL-C and decreased LDL-C in patients with metabolic syndrome[92]. The oral treatment of *N. sativa* powder in hypercholesterolemia patients at the dose of 1 g daily before breakfast for two months significantly reduced serum levels of TC, LDL and TG, and increase HDL[96]. In addition, serum TC, LDL and TG were reduced significantly after 6 mo of treatment with *N. sativa* powder (500 mg) and statin (10-20 mg) in patients with stable coronary artery disease in Multan, Pakistan compared to group receiving statin (10-20 mg) alone[97]. The effect of oral treatment of *N. sativa* seed in male patients with mild dyslipidaemia and hypertension was also investigated for a period of eight weeks. Patients were randomized into three groups: a placebo and two test groups that received 100 and 200 mg of *N. sativa* extract twice a day. The results showed a significant dose-dependent decline in the serum levels of TC, TG, LDL, SBP, and DBP in *N. sativa* extract groups[91].

The effect of *N. sativa* on the blood levels of glucose, uric acid, TG, cholesterol, blood urea nitrogen (BUN) and creatinine in normal healthy human subjects was evaluated in two groups, I) test group received *N. sativa* powder (500 mg) capsules, II) the placebo group received the placebo capsules (brown sugar,

500 mg) twice daily. The results indicated that *N. sativa* significantly reduced blood levels of glucose and cholesterol[98]. Favourable effects of the capsulated *N. sativa* powder (500 mg) on blood pressure, serum total cholesterol, LDL cholesterol, triglycerides, and fasting blood sugar have also been reported in another human study but results were not statistically significant because of small sample size[99]. The effects *N. sativa* supplementation (2 g/day) and aerobic training on lipid profile in sedentary overweight females for a period of eight weeks also indicated that the combination of the plant and aerobic exercise caused significant improvements in serum LDL-C and HDL-C[100]. In addition, administration of 200 mg *N. sativa* seed twice daily for three months in patients with ischemic heart disease also significantly reduced TG and increased HDL-C[101].

The effect of 2.5 ml *N. sativa* seed oil twice daily in comparison to atorvastatin 10 mg once a day, metformin 500 mg twice a day, atenolol 50 mg once a day, amlodipine 5 mg once a day for a period of six weeks in patients with metabolic syndrome showed that treatment with *N. sativa* significantly decreased serum levels of LDL-C and increased HDL-C[102]. The supplementation of 2.5 ml *N. sativa* seed oil twice a day for a period of eight weeks significantly reduced fasting blood cholesterol, LDL, TG, glucose and HbA1C levels in healthy subjects[103]. Furthermore, administration of 3 g/day *N. sativa* seed oil for two months significantly reduced TG, VLDL, weight and waist circumference in obese women[104].

Treatment with *N. sativa* 2 g/day for 4 w in hyperlipidemia patients showed significant decrease in serum levels of TC, TG and LDL[105]. Saboos-e-Asapghol (*Plantago ovata*) 4 g and *N. sativa* 2 g twice daily for a period of 90 d in patients with hypertriglyceridemia also significantly reduced serum TG level[106]. The effect of *N. sativa* seed oil (100, 140 ng/ml) on regulation of primary human monocyte growth and CD11b expression showed that *N. sativa*

TABLE 5: CLINICAL EFFECTS OF *N. SATIVA* AND ITS CONSTITUENTS ON LIPID PROFILE

Plant preparation	Study model	Effect	Reference
N. sativa	Hyperlipidemia patients	Decreased TC, TG and LDL	[105]
N. sativa	Hyperlipidemia patients	Reduced LDL-C, increased HDL-C	[107]
N. sativa	Normal healthy human	Reduced blood levels of both glucose and cholesterol	[98]
N. sativa seed powder	Menopausal women	Increased HDL-C, decreased LDL-C, TC, TG and FBG	[95]
N. sativa powder	Hypercholesterolemia patients	Reduced TC, LDL and TG, increased HDL	[96]
N. sativa powder	Patients with stable coronary artery disease	Reduced TC, LDL and TG	[97]
N. sativa seed	Patients with mild hyperlipidemia and hypertension	Significant dose-dependent decline in the levels of TC, TG ,LDL	[91]
N. sativa seed	Patients with ischemic heart disease	Reduced TG Increased HDL-C	[101]
N. sativa seed	Hyperlipidemia patients	Reduced TC, TG, LDL-C, increased HDL-C	[108]
N. sativa seed oil	Normal healthy human	Reduced fasting blood cholesterol, LDL, TG, glucose and HbA1C levels	[103]
N. sativa seed oil	Obese women	Reduced TG, VLDL, weight and waist circumference	[104]
N. sativa oil	Patients with metabolic syndrome	Decreased LDL-C, increased HDL-C	[102]
N. sativa oil	Patients with metabolic syndrome	Decreased LDL-C, increased HDL	[92]
N. sativa seeds and honey mixture	Hypercholesterolemia patients	Decreased TC, TG, TC:HDL-c, increased HDL-c	[94]
N. sativa seeds, garlic oil and simvastatin	Patients with dyslipidemia	Reduced TC, TG, LDL-C, Non-HDL, increased HDL-C	[110]
N. sativa and aerobic exercise	Sedentary overweight females	Improved LDL−C and HDL-C	[100]
N. sativa and Saboos-e-Asapghol	Hypertriglyceridemia patients	Reduced TG	[106]

TG: triglyceride, TC: total cholesterol, VLDL: very low-density lipoprotein, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, FBG: fasting blood glucose, HbA1C: hemoglobin A1C

seed oil provided preliminary support on regulation of cell growth and differentiation in monocyte and monocyte-derived macrophages and reduced CD11b expression[107]. Two tea spoons (approximately 9.0 g)/ day *N. sativa* seed compared to gemfibrozil 600 mg twice daily for a period of eight weeks in hyperlipidemia patients significantly reduced serum levels of TC, TG, and LDL-C and increased HDL-C[108].

The effects of *N. sativa* in comparison to nicotinic acid along with low fat diet and physical exercise in hyperlipidemia patients divided to three groups: I) placebo group, II) 2 tea spoons *N. sativa* after breakfast, and III) niacin 2 g in divided doses, after breakfast, lunch and dinner for the period of two months was investigated. The results showed that *N. sativa* and niacin significantly reduced serum level of LDL-C and increased HDL-C in hyperlipidemia patients[109].

Combination therapy of *N. sativa* seeds (50 mg/kg) and honey significantly decreased serum TC, TG, TC: HDL-C, as well as SBP, DBP and increased HDL-C in hypercholesterolemia[94]. Combination treatment of *N. sativa* seeds (500 mg), garlic oil (250 mg) and simvastatin (10 mg) capsule once daily after meal at night significantly reduced serum TC, TG, LDL-C, and Non-HDL and elevated HDL-C in dyslipidemia patients[110]. The effects of *N. sativa* and its constituents on lipid profile in human studies were shown in Table 5.

From various reports, it is concluded that *N. sativa* and its main constituent's, TQ showed antihypertensive, antiatherogenic, antihyperlipidemic, hypoglycemic and cardioprotective effects. The results of reviewed articles indicated the preventive and therapeutic effects of *N. sativa* and its constituents on cardiovascular diseases. However, further investigations are required to reveal the exact perspectives of molecular and cellular basis of *N. sativa* and its constituent's effects on cardiovascular disorders. In addition further clinical investigations also needed to be conducted regarding the effect of the plant and its constituents on cardiovascular disorders.

Conflicts of interest:

There are no conflicts of interest among the authors.

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