

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*. It seems that *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], antioxytotic^[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 CO₂ 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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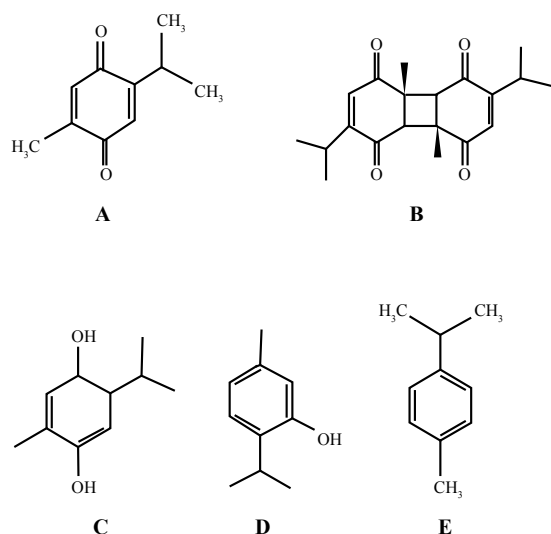


Fig. 1: Chemical structure of some potentially bioactive compounds in *N. sativa*
A: Thymoquinone; B: dithymoquinone; C: thymohydroquinone; D: thymol; E: p-cymene

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]. Dethymoquinone 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
<i>N. sativa</i> and honey	Sodium nitrite and sunset yellow-induced heart disorder	Modulating heart disorder induced by food additives	[33]
<i>N. sativa</i> oil	Lead-induced cardiotoxicity in rat	Decreased heart rate, ST segment change, pro inflammatory cytokines, oxidative stress and cardiac tissue damage	[34]
<i>N. sativa</i> oil	Cyclosporine A-induced cardiomyopathy in rat	Normalized cardiac histopathology, decreased lipid peroxidation, improved antioxidant enzyme status and cellular protein oxidation	[35]
<i>N. sativa</i> 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]
<i>N. sativa</i>	RVH model in rat	Reduced BP, oxidative injury, improved left ventricular function	[43]
<i>N. sativa</i>	L-NAME-induced hypertension in rat	Reduced SBP and DBP	[44]
<i>N. sativa</i> and <i>S. aromaticum</i> extract	L-NAME-induced hypertension in rat	Reduced SBP, DBP, MAP, LDL, increased serum nitric oxide	[47]
Aqueous extract	Spontaneously hypertensive rat	Reduced SBP	[46]
Dichloromethane extract	Spontaneously hypertensive rat	Increased urinary output and glomerular filtration rate	[46]
Volatile oil	Normotensive guinea pigs	Increased the diuresis, reduced MAP	[6]
Volatile oil and TQ	Urethane-anaesthetized rat	Reduced BP and heart rate in a dose dependent manner	[45]
Alpha-pinene	Non-anaesthetized normotensive rat	Decreased arterial blood pressure and heart rate in a dose-dependent manner	[5]
Dethymoquinonated volatile of <i>N. sativa</i> , α -pinene and p-cymene	Urethane-anaesthetized rat	Hypotensive effect	[49]
TQ	L-NAME-induced hypertension in rat	Reduced BP and heart rate	[50]
		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 <i>N. sativa</i>	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]
<i>N. sativa</i>	The intrinsic cardiac responses	Increased left ventricular and whole heart weights, improved baseline peak tension heart rate and myocardial flow rate	[55]
<i>N. sativa</i>	Cardiac reserve in rats	Increase heart weight to body weight ratio and baseline cardiac inotropic properties	[57]
<i>N. sativa</i>	<i>N. sativa</i> supplementation and exercise training in rat	Cardiac hypertrophy, reduced heart rate	[58-59]
<i>N. sativa</i>	Myocardial ischemic reperfusion injury in rat	Increased contractile and vascular functions, reduced oxidative stress in cardiac tissue	[60]
<i>N. sativa</i>	Cadmium-treated rats	Decreased heart rate, glucose concentration, increased RBC, WBC counts, Hb, and PCV.	[61]
<i>N. sativa</i>	Alloxan-induced diabetic rabbits	Reduced heart rate	[62]
<i>N. sativa</i> 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 <i>N. sativa</i>	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
<i>N. sativa</i>	Rat	Increased HDL-C, decreased LDL-C	[81]
<i>N. sativa</i>	Rat fed with palm oil	Reduced TC and LDL-C, increased HDL-C	[82,83]
<i>N. sativa</i>	Rat fed with cholesterol rich diet	Reduced TC, TG, LDL-C, increased HDL-C	[70,71]
<i>N. sativa</i>	Hyperlipidemia rabbit	Reduced TC, TG, LDL-C, MDA	[72]
<i>N. sativa</i>	Hypercholesterolemia rabbit	Reduced TC and LDL-C	[73]
<i>N. sativa</i>	Sunflower oil, cholic acid and propylthiouracil diet in rat	Reduced TC, TG, LDL-C, increased HDL-C	[74]
<i>N. sativa</i>	Rat	Reduced TC, LDL, TG, increased HDL/LDL ratio	[68]
<i>N. sativa</i> and olive oil	Hyperlipidemia mice	Reduced TC, TG, LDL-C and VLDL-C, increased HDL-C	[76]
<i>N. sativa</i> seed	Pekin ducklings	Reduced HDL-C, elevated TC, TG, LDL-C, VLDL-C	[79]
<i>N. sativa</i> seed powder and Canola oil	Rat	Reduced TC and LDL-C	[80]
<i>N. sativa</i> seed fixed oil	Rat	Reduced TC, TG, glucose levels, leukocytes and platelets counts, increased hematocrit and hemoglobin levels	[66]
<i>N. sativa</i> oil	Sheep	Increased TC, TG, LDL-C, HDL-C	[78]
<i>N. sativa</i> oil	Rat	Decrease TC, LDL, TG, increased HDL	[67]
Methanolic extract and volatile oil of <i>N. sativa</i>	Hyperlipidemia rat	Reduced TG, TC, VLDL-C, LDL-C, HMG-CoA reductase activity, increased HDL-c	[64]
Petroleum ether extract of <i>N. sativa</i> seeds	Rat	Reduced fasting plasma levels of insulin and TG, increased HDL-C	[65]
Ethanol extract of <i>N. sativa</i> 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 <i>N. sativa</i>	An animal model of menopause	Reduced blood glucose and LDL-C	[75]
Acetone extract and <i>N. sativa</i> 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
<i>N. sativa</i>	Hypercholesterolemia rabbit	Decreased TC, LDL-C and fatty streak formation	[88,89]
<i>N. sativa</i> seeds powder	Hypercholesterolemia rabbit	Reduced TC, TG, LDL-C, increased HDL-C	[87]
<i>N. sativa</i> 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 <i>N. sativa</i> 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]
<i>N. sativa</i> seed	Patients with mild hyperlipidemia and hypertension	Dose-dependent decline in SBP and DBP	[91]
<i>N. sativa</i> oil	Patients with metabolic syndrome	Decreased SBP, DBP	[92]
<i>N. sativa</i> oil	Normal healthy human	Decreased SBP and DBP	[93]
<i>N. sativa</i> 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
<i>N. sativa</i>	Hyperlipidemia patients	Decreased TC, TG and LDL	[105]
<i>N. sativa</i>	Hyperlipidemia patients	Reduced LDL-C, increased HDL-C	[107]
<i>N. sativa</i>	Normal healthy human	Reduced blood levels of both glucose and cholesterol	[98]
<i>N. sativa</i> seed powder	Menopausal women	Increased HDL-C, decreased LDL-C, TC, TG and FBG	[95]
<i>N. sativa</i> powder	Hypercholesterolemia patients	Reduced TC, LDL and TG, increased HDL	[96]
<i>N. sativa</i> powder	Patients with stable coronary artery disease	Reduced TC, LDL and TG	[97]
<i>N. sativa</i> seed	Patients with mild hyperlipidemia and hypertension	Significant dose-dependent decline in the levels of TC, TG, LDL	[91]
<i>N. sativa</i> seed	Patients with ischemic heart disease	Reduced TG	[101]
<i>N. sativa</i> seed	Hyperlipidemia patients	Increased HDL-C	[108]
<i>N. sativa</i> seed oil	Normal healthy human	Reduced fasting blood cholesterol, LDL, TG, glucose and HbA1C levels	[103]
<i>N. sativa</i> seed oil	Obese women	Reduced TG, VLDL, weight and waist circumference	[104]
<i>N. sativa</i> oil	Patients with metabolic syndrome	Decreased LDL-C, increased HDL-C	[102]
<i>N. sativa</i> oil	Patients with metabolic syndrome	Decreased LDL-C, increased HDL	[92]
<i>N. sativa</i> seeds and honey mixture	Hypercholesterolemia patients	Decreased TC, TG, TC:HDL-c, increased HDL-c	[94]
<i>N. sativa</i> seeds, garlic oil and simvastatin	Patients with dyslipidemia	Reduced TC, TG, LDL-C, Non-HDL, increased HDL-C	[110]
<i>N. sativa</i> and aerobic exercise	Sedentary overweight females	Improved LDL-C and HDL-C	[100]
<i>N. sativa</i> 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.

REFERENCES

1. Khare CP. Encyclopedia of Indian medicinal plants. New York: Springers-Verlag Berlin Heidelberg; 2004.
2. Chakravarty N. Inhibition of histamine release from mast cells by nigellone. *Ann Allergy* 1993;70:237-42.
3. Mahfouz M, Abdelmag R, Ekhak M. The effect of "nigellone therapy" on the histaminopexic power of the blood sera in asthmatic patients. *Drug Res* 1965;15:1230-4.
4. Boskabady MH, Shahabi M. Bronchodilatory and anticholinergic effects of *Nigella sativa* on isolated guinea-pig tracheal chains. *Iran J Med Sci* 1997;22:127-33.
5. El Tahir KE, Ashour MM, Al-Harbi MM. The cardiovascular actions of the volatile oil of the black seed (*Nigella sativa*) in rats: elucidation of the mechanism of action. *Gen Pharmacol* 1993;24:1123-31.
6. Zaoui A, Cherrah Y, Lacaille-Dubois M, Settaf A, Amarouch H, Hassar M. Diuretic and hypotensive effects of *Nigella sativa* in the spontaneously hypertensive rat. *Therapie* 1999;55:379-82.
7. Al-Hader A, Aqel M, Hasan Z. Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. *IntJ Pharmacogn* 1993;31:96-100.
8. Aqel M, Shaheen R. Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig. *J Ethnopharmacol* 1996;52:23-6.
9. Abdel-Fattah AM, Matsumoto K, Watanabe H. Antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, in mice. *Eur J Pharmacol* 2000;400:89-97.
10. el Tahir KE, Ashour MM, al-Harbi MM. The respiratory effects of the volatile oil of the black seed (*Nigella sativa*) in guinea-pigs: elucidation of the mechanism (s) of action. *Gen Pharmacol* 1993;24:1115-22.
11. Boskabady MH, Javan H, Sajady M, Rakhshandeh H. The possible prophylactic effect of *Nigella sativa* seed extract in asthmatic patients. *Fundam Clin Pharmacol* 2007;21:559-66.
12. Boskabady MH, Kiani S, Jandaghi P. Antitussive effect of *Nigella sativa* in guinea pigs. *Pak J Med Sci* 2004;20:224-8.
13. Boskabady MH, Mohsenpoor N, Takaloo L. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomedicine* 2010;17:707-13.
14. Boskabady MH, Keyhanmanesh R, Ebrahimi Saadatloo MA. Relaxant effects of different fractions from *Nigella sativa* L. on guinea pig tracheal chains and its possible mechanism (s). *Indian J Exp Biol* 2008;46:805-10.
15. Boskabady MH, Shirmohammadi B, Jandaghi P, Kiani S. Possible mechanism (s) for relaxant effect of aqueous and macerated extracts from *Nigella sativa* on tracheal chains of guinea pig. *BMC Pharmacol* 2004;4:1-6.
16. Enomoto S, Asano R, Iwahori Y, Narui T, Okada Y, Singab AN, et al. Hematological studies on black cumin oil from the seeds of *Nigella sativa* L. *Biol Pharm Bull* 2001;24:307-10.
17. Daba MH, Abdel-Rahman MS. Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. *Toxicol Lett* 1998;95:23-9.
18. Swamy S, Tan B. Cytotoxic and immunopotentiating effects of ethanolic extract of *Nigella sativa* L. seeds. *J Ethnopharmacol* 2000;70:1-7.
19. Al-Sheddi ES, Farshori NN, Al-Oqail MM, Musarrat J, Al-Khedhairi AA, Siddiqui MA. Cytotoxicity of *Nigella sativa* seed oil and extract against human lung cancer cell line. *Asian Pac J Cancer Prev* 2014;15:983-7.
20. Landa P, Marsik P, Havlik J, Kloucek P, Vanek T, Kokoska L. Evaluation of antimicrobial and anti-inflammatory activities of seed extracts from six *Nigella* species. *J Med Food* 2009;12:408-15.

21. Rakhshandeh H, Vahdati-Mashhadian N. *In vitro* and *in vivo* study of the antibacterial effects of *Nigella sativa* methanol extract in dairy cow mastitis. *Avicenna J Phytomed* 2011;1:29-35.
22. Khan MA, Ashfaq MK, Zuberi HS, Mahmood MS, Gilani AH. The *in vivo* antifungal activity of the aqueous extract from *Nigella sativa* seeds. *Phytother Res* 2003;17:183-6.
23. Akhtar AH, Ahmad KD, Gilani SD, Nazir A. Antiulcer effects of aqueous extracts of *Nigella sativa* and *Pongamia pinnata* in rats. *Fitoterapia* 1996;67:195-9.
24. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. *Int Immunopharmacol* 2005;5:1749-70.
25. Boulos L. *Medicinal Plants of North Africa*. Algonac, Michigan: Reference Publications, Inc.; 1983.
26. Venkatachallam ST, Pattekhani H, Divakar S, Sankar Kadimi U. Chemical composition of *Nigella sativa* L. seed extracts obtained by supercritical carbon dioxide. *J Food Sci Technol* 2010;47:598-65.
27. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, *et al.* A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Biomed* 2013;3:337-52.
28. Alimohammadi S, Hobbenaghi R, Javanbakht J, Kheradmand D, Mortezaee R, Tavakoli M, *et al.* Protective and antidiabetic effects of extract from *Nigella sativa* on blood glucose concentrations against streptozotocin (STZ)-induced diabetic in rats: an experimental study with histopathological evaluation. *Diagn Pathol* 2013;8:1-7.
29. Gilani AH, Shaheen F, Shakir T. Thymol lowers blood pressure through blockade of calcium channels. *Fundam Clin Pharmacol* 2001;15:163.
30. Peixoto-Neves D, Silva-Alves K, Gomes M, Lima FC, Lahlou S, Magalhães PJ, *et al.* Vasorelaxant effects of the monoterpene phenol isomers, carvacrol and thymol, on rat isolated aorta. *Fundam Clin Pharmacol* 2010;24:341-50.
31. Boskabady MH, Shafei M, Parsaee H. Effects of aqueous and macerated extracts from *Nigella sativa* on guinea pig isolated heart activity. *Pharmazie* 2005;60:943-8.
32. Shafei MN, Boskabady MH, Parsaee H. Effect of aqueous extract from *Nigella sativa* L. on guinea pig isolated heart. *Indian J Exp Biol* 2005;43:635-9.
33. El-Kholy WM, Hassan HA, Nour SE. The role of black seed and/or bees honey in modulating the heart disorder induced by food additives in male rats. *Egypt J Hosp Med* 2007;28:327-41.
34. Ahmed MA, Hassanein KM. Cardioprotective effects of *Nigella sativa* oil on lead induced cardiotoxicity: Anti inflammatory and antioxidant mechanism. *J Physiol Pathophysiol* 2013;4:72-80.
35. Ebru U, Burak U, Yusuf S, Reyhan B, Arif K, Faruk TH, *et al.* Cardioprotective effects of *Nigella sativa* oil on cyclosporine A-induced cardiotoxicity in rats. *Basic Clin Pharmacol Toxicol* 2008;103:574-80.
36. El-Saleh SC, Al-Sagair OA, Al-Khalaf MI. Thymoquinone and *Nigella sativa* oil protection against methionine-induced hyperhomocysteinemia in rats. *Int J Cardiol* 2004;93:19-23.
37. Nagi MN, Al-Shabanah OA, Hafez MM, Sayed-Ahmed MM. Thymoquinone supplementation attenuates cyclophosphamide-induced cardiotoxicity in rats. *J Biochem Mol Toxicol* 2011;25:135-42.
38. al-Shabanah OA, Badary OA, Nagi MN, al-Gharably NM, al-Rikabi AC, al-Bekairi AM. Thymoquinone protects against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. *J Exp Clin Cancer Res* 1998;17:193-8.
39. Nagi MN, Mansour MA. Protective effect of thymoquinone against doxorubicin-induced cardiotoxicity in rats: A possible mechanism of protection. *Pharmacol Res* 2000;41:283-9.
40. Ince S, Kucukkurt I, Demirel HH, Turkmena R, Sever E. Thymoquinone attenuates cypermethrin induced oxidative stress in swiss albino mice. *Pest Biochem Physiol* 2012;104:229-35.
41. Nemmar A, Al-Salam S, Zia S, Marzouqi F, Al-Dhaheri A, Subramaniyan D, *et al.* Contrasting actions of diesel exhaust particles on the pulmonary and cardiovascular systems and the effects of thymoquinone. *Br J Pharmacol* 2011;164:1871-82.
42. Randhawa MA, Alghamdi MS, Maulik SK. The effect of thymoquinone, an active component of *Nigella sativa*, on isoproterenol induced myocardial injury. *Pak J Pharm Sci* 2013;26:1215-9.
43. Tasar N, Sehirlı O, Yiginer O, Soleymanoglu S, Yoksel M, Yegen B, *et al.* Protective effects of *Nigella sativa* against hypertension-induced oxidative stress and cardiovascular dysfunction in rats. *J Res Pharm* 2012;16:141-9.
44. Jaarin K, Kamisah Y, Muhammad FONA, Jubri Z, Saad QM, Das S. Effect of *Nigella Sativa* on Blood Pressure, Vascular Reactivity, Inflammatory Biomarkers and Nitric Oxide in L-Name-Induced Hypertensive Rats. *Int J Bioeng Life Sci* 2014;1:259-65.
45. El Tahir KE, Ageel A. Effect of the volatile oil of *Nigella sativa* on the arterial blood pressure and heart rate of the guinea-pig. *Saudi Pharm J* 1994;2:163-8.
46. Zeggwagh N, Moufid A, Khaldi A, Michel JB, Eddouks M, Singh VK, *et al.* Cardiovascular effect of *Nigella sativa* aqueous extract in spontaneously hypertensive rats. *Chem Med J* 2009;25:243-52.
47. Sayed HM, El-Latif HAA, Eid NI, Elsayed AZ, El-Kader EMA. Potential antihypertensive and antioxidative effects of *Nigella sativa* seeds or biomass and *Syzygium aromaticum* extracts on L-NAME-induced hypertensive rats. *Egypt Pharmaceut J* 2009;50:127-46.
48. Khattab MM, Nagi MN. Thymoquinone supplementation attenuates hypertension and renal damage in nitric oxide deficient hypertensive rats. *Phytother Res* 2007;21:410-4.
49. Menezes IA, Barreto C, Antonioli AR, Santos MR, de Sousa DP. Hypotensive activity of terpenes found in essential oils. *Z Naturforsch C* 2010;65:562-6.
50. Eh EK, Al-Ajmi M, Al-Bekairi A. Some cardiovascular effects of the dethymoquinonated *Nigella sativa* volatile oil and its major components α -pinene and p-cymene in rats. *Saudi Pharm J* 2003;11:104-10.
51. Agarwal R, Kharya M, Shrivastava R. Pharmacological studies of essential oil and unsaponifiable matter of seeds of *Nigella sativa*. *Indian J Pharmacol Sci* 1979;41:248-510.
52. Niazmand S, Fereidouni E, Mahmoudabady M, Mousavi SM. Endothelium-Independent Vasorelaxant Effects of Hydroalcoholic Extract from *Nigella sativa* Seed in Rat Aorta: The Roles of Ca²⁺. *BioMed Res Int* 2014;2014:1-7.
53. Suddek GM. Thymoquinone-induced relaxation of isolated rat pulmonary artery. *J Ethnopharmacol* 2010;127:210-4.
54. Idris-Khodja N, Schini-Kerth V. Thymoquinone improves aging-related endothelial dysfunction in the rat mesenteric artery. *Naunyn Schmiedeberg Arch Pharmacol* 2012;385:749-58.
55. El-Bahai M, Al-Hariri M, Yar T, Bamasa AO. Cardiac inotropic

- and hypertrophic effects of *Nigella sativa* supplementation in rats. *Int J Cardiol* 2009;131:115-7.
56. Al-Hariri MT, Yar T, Bamosa AO, El-Bahai MN. Effects of two-months *Nigella sativa* supplementation on cardiac haemodynamics and adrenergic responsiveness. *J Pak Med Assoc* 2009;59:363-8.
 57. Yar T, El-Hariri M, El-Bahai M, Bamosa AO. Effects of *Nigella sativa* supplementation for one month on cardiac reserve in rats. *Indian J Physiol Pharmacol* 2008;52:141-8.
 58. Al-Asoom LI, Al-Shaikh BA, Bamosa AO, El-Bahai MN. Effect of *Nigella sativa* supplementation to Exercise Training in a Novel Model of Physiological Cardiac Hypertrophy. *Cardiovasc Toxicol* 2014;14:243-50.
 59. Al-Asoom LI, Al-Shaikh BA, Bamosa AO, El-Bahai MN. Comparison of *Nigella sativa* and Exercise-Induced Models of Cardiac Hypertrophy: Structural and Electrophysiological Features. *Cardiovasc Toxicol* 2014;14:208-13.
 60. Seif AA. *Nigella sativa* attenuates myocardial ischemic reperfusion injury in rats. *J Physiol Biochem* 2013;69:937-44.
 61. Demir H, Kanter M, Coskun O, Uz YH, Koc A, Yildiz A. Effect of black cumin (*Nigella sativa*) on heart rate, some hematological values, and pancreatic β -cell damage in cadmium-treated rats. *Biol Trace Elem Res* 2006;110:51-62.
 62. Meral I, Donmez N, Baydas B, Belge F, Kanter M. Effect of *Nigella sativa* L. on heart rate and some haematological values of alloxan-induced diabetic rabbits. *Scand J Lab Anim Sci* 2004;31:49-53.
 63. Vijayalakshmi P, Rajarajeswari A, Mohamed SA. Cardioprotective effect of *Nigella sativa* seed and oil on Isoproterenol induced myocardial infarction in Rats. *Bioascan* 2012;7:143-7.
 64. Ahmad S, Beg ZH. Elucidation of mechanisms of actions of thymoquinone-enriched methanolic and volatile oil extracts from *Nigella sativa* against cardiovascular risk parameters in experimental hyperlipidemia. *Lipids Health Dis* 2013;12:1-12.
 65. Le PM, Benhaddou-Andaloussi A, Elimadi A, Settaf A, Cherrah Y, Haddad PS. The petroleum ether extract of *Nigella sativa* exerts lipid-lowering and insulin-sensitizing actions in the rat. *J Ethnopharmacol* 2004;94:251-9.
 66. Zaoui A, Cherrah Y, Alaoui K, Mahassine N, Amarouch H, Hassar M. Effects of *Nigella sativa* fixed oil on blood homeostasis in rat. *J Ethnopharmacol* 2002;79:23-6.
 67. el-Dakhkhny M, Mady NI, Halim MA. *Nigella sativa* L. oil protects against induced hepatotoxicity and improves serum lipid profile in rats. *Arzneimittelforschung* 2000;50:832-6.
 68. Ali BA, Bamosa AO, Al-Hawsawi Z. Effect of *Nigella sativa* on blood lipids in normal rats. *Arab Gulf J Sci Res* 2003;21:102-9.
 69. Ali Y, Islam MS, Alam AHMK, Rahman MAA, Mamun AI, Hossain MK, et al. Inhibitory Effects of *Nigella sativa* Seed Extract on Adrenaline-Induced Dyslipidemia and Left Ventricular Hypertrophy in Rats. *J Sci Res* 2013;5:325-34.
 70. Muneera KE, Majeed A, Naveed AK. Comparative evaluation of *Nigella sativa* (Kalonji) and simvastatin for the treatment of hyperlipidemia and in the induction of hepatotoxicity. *Pak J Pharm Sci* 2015;28:493-8.
 71. Kirn-E-Muneera MaS, Abdul Khaliq N, Asifa M, Hussain A. Efficacy of *Nigella sativa* (Kalongi) for the Treatment of Hyperlipidemia in Sprague Dawley Rats. *J Rawalpindi Med Coll* 2013;17:144-7.
 72. Pourghassem-Gargari B, Ebrahimzadeh-Attary V, Rafrat M, Gorbani A. Effect of dietary supplementation with *Nigella sativa* L. on serum lipid profile, lipid peroxidation and antioxidant defense system in hyperlipidemic rabbits. *J Med Plant Res* 2009;3:815-21.
 73. Asgary S, Ghannadi A, Dashti G, Helalat A, Sahebkar AH, Najafi S. *Nigella sativa* L. improves lipid profile and prevents atherosclerosis: Evidence from an experimental study on hypercholesterolemic rabbits. *J Funct Foods* 2013;5:228-34.
 74. Buriro MA, Tayyab M. Effect of *Nigella sativa* on lipid profile in albino rats. *Gomal J Med Sci* 2007;5:28-31.
 75. Parhizkar S, Latiff LA, Rahman SA, Hanachi P, Aziz Dollah M. Metabolic Impact of *Nigella sativa* extracts on Experimental Menopause Induced Rats. *J Appl Pharm Sci* 2011;1:38-42.
 76. Kafi LA. A comparative study between olive oil and *Nigella Sativa* oil in treatment of hyperlipidemia induced in male albino mice. *Iraqi J Vet Med Sci* 2014;38:123-7.
 77. Siddiqui MN, Islam M, Sayed M, Hossain MA. Effect of dietary supplementation of acetone extracts of *Nigella sativa* L. seeds on serum cholesterol and pathogenic intestinal bacterial count in broilers. *J Anim Plant Sci* 2015;25:372-9.
 78. Maha IH, Nabeila E-BM, Al-Tayib O. Effect of commercial oil of *Nigella sativa* L. seeds on lipids parameters and weight in sheep. *J Pharm Innov* 2013;3:87-91.
 79. El-Bahr SM. Effect of black cumin seeds (*Nigella sativa*) on the profile of serum lipids, lipoproteins and fatty acids in pekin ducklings. *Int J Appl Chem* 2007;3:221.
 80. Ahmed M, Kousar N, Abid SM, Farooq M. Effect of canol oil supplemented with atherogenic element and *Nigella sativa* on serum lipids in albino rats. *Pak Armed Forces Med J* 2015;65:243-6.
 81. Dahri AH, Chandiol A, Rahoo AA, Memon RA. Effect of *Nigella sativa* (kalonji) on serum cholesterol of albino rats. *J Ayub Med Coll Abbottabad* 2005;17:72-4.
 82. Iqbal Z, Sattar A, Haider S, Tayyab M, Chaudhry NA. Morphological Changes in Aorta and Coronary Arteries of Albino Rats Fed on Palm Kernel Oil and *Nigella Sativa*. *Pak J Med Health Sci* 2013;7:111-3.
 83. Iqbal Z, Soomro AA, Shah NA, Sattar A. Effect of Palm Oil and *Nigella Sativa* in Aorta and Coronary Arteries of Albino Rats. *Pak J Med Health Sci* 2013;7:804-7.
 84. Ragheb A, Attia A, Elbarbry F, Prasad K, Shoker A. Attenuated combined action of cyclosporine A and hyperlipidemia on atherogenesis in rabbits by thymoquinone. *Evid Based Complement Alternat Med* 2011;2011:1-9.
 85. Ragheb A, Elbarbry F, Prasad K, Mohamed A, Ahmed MS, Shoker A. Attenuation of the development of hypercholesterolemic atherosclerosis by thymoquinone. *Int J Angiol* 2008;17:186-92.
 86. Al-Naqeep G, Al-Zubairi AS, Ismail M, Amom ZH, Esa NM. Antiatherogenic potential of *Nigella sativa* seeds and oil in diet-induced hypercholesterolemia in rabbits. *Evid Based Complementary Altern Med* 2011;2011:1-8.
 87. Fatima S, Khan N, Naz L, Yasmeen G, Hajira B, Hussain Z. Antiatherogenic effect of *Nigella sativa* L.(Kalonji) seeds in rabbits with experimentally-induced hypercholesterolemia. *Int J Biol Biotechnol* 2007;437-41.
 88. Asgari S, Ghandi A, Adibi S, Dashti GR, Naderi GA, Helalat AR, et al. The effects of *Nigella sativa* on atherosclerosis and its new risk factors in hypercholesterolemic rabbits. *Iranian J Diabetes Metab* 2007;6:235-42.
 89. Asgary S, Ghannadi A, Dashti G, Helalat A, Najafi S. Preventive potential of *Nigella sativa* L. on atherosclerosis

- with efficacy on lipid profile and fatty streak accumulation in diet-induced hypercholesterolemia in rabbits. *Res Pharm Sci* 2012;7:10-3.
90. Nader MA, el-Agamy DS, Suddek GM. Protective effects of propolis and thymoquinone on development of atherosclerosis in cholesterol-fed rabbits. *Arch Pharm Res* 2010;33:637-43.
 91. Dehkordi FR, Kamkhah AF. Antihypertensive effect of *Nigella sativa* seed extract in patients with mild hypertension. *Fundam Clin Pharmacol* 2008;22:447-52.
 92. Nanjmi A, Nasiruddin M, Khan R, Haque SF. Indigenous herbal product *Nigella sativa* proved effective as an antihypertensive in metabolic syndrome. *Asian J Pharm Clin Res* 2013;6:61-4.
 93. Fallah Huseini H, Amini M, Mohtashami R, Ghamarchehre ME, Sadeqhi Z, Kianbakht S, *et al.* Blood Pressure Lowering Effect of *Nigella sativa* L. Seed Oil in Healthy Volunteers: A Randomized, Double-Blind, Placebo-controlled Clinical Trial. *Phytother Res* 2013;27:1849-53.
 94. Mohamad S, Ibrahim NH, Yusof H. Blood Pressure and Lipid Lowering Effects of *Nigella sativa* Seeds and Honey Mixture. *Nurs Health Sci* 2014;3:89-96.
 95. Ibrahim RM, Hamdan NS, Mahmud R, Imam MU, Saini SM, Rashid SN, *et al.* A randomised controlled trial on hypolipidemic effects of *Nigella sativa* seeds powder in menopausal women. *J Transl Med* 2014;12:1-7.
 96. Bhatti IU, Ur Rehman F, Khan MA, Khan Marwat S. Effect of prophetic medicine kalonji (*Nigella sativa* L.) on lipid profile of human beings. An *in vivo* approach. *World Appl Sci J* 2009;6:1053-7.
 97. Tasawar Z, Siraj Z, Ahmad N, Mushtaq HL. The effects of *Nigella sativa* (Kalonji) on lipid profile in patients with stable coronary artery disease in Multan, Pakistan. *Pak J Nutr* 2011;10:162-7.
 98. Bamosa AO, Ali BA, Sowayan S. Effect of oral ingestion *Nigella sativa* seeds on some blood parameters. *Saudi Pharm J* 1997;5:126-9.
 99. Qidwai W, Hamza HB, Qureshi R, Gilani A. Effectiveness, safety, and tolerability of powdered *Nigella sativa* (kalonji) seed in capsules on serum lipid levels, blood sugar, blood pressure, and body weight in adults: results of a randomized, double-blind controlled trial. *J Altern Complement Med* 2009;15:639-44.
 100. Farzaneh E, Nia FR, Mehrtash M, Mirmoeini FS, Jalilvand M. The effects of 8-week *Nigella sativa* supplementation and aerobic training on lipid profile and VO₂ max in sedentary overweight females. *Int J Prev Med* 2014;5:210-6.
 101. Zaki A. Study of the effect of *Nigella sativa* seeds on serum level of glucose and some lipoprotein fractions in patients with ischemic heart disease. *J Med Res* 2005;26:15-19.
 102. Najmi AH, Shahzad F, Khan Rahat Ali, Haque SF. Therapeutic Effect of *Nigella Sativa* oil on Different Clinical And Biochemical Parameters In Metabolic Syndrome. *Internet J Pharmacol* 2008;5:1-8.
 103. Amini M, Fallah Huseini H, Mohtashami R, Sadeqhi Z, Ghamarchehre MA. Hypolipidemic Effects of *Nigella sativa* L. Seeds Oil in Healthy Volunteers: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *J Med Plants* 2011;4:133-8.
 104. Mahdavi R, Namazi N, Alizadeh M, Farajnia S. Effects of *Nigella sativa* oil with a low-calorie diet on cardiometabolic risk factors in obese women: a randomized controlled clinical trial. *Food Funct* 2015;6:2041-8.
 105. Sabzghabae AM, Dianatkah M, Sarrafzadegan N, Asgary S, Ghannadi A. Clinical evaluation of *Nigella sativa* seeds for the treatment of hyperlipidemia: a randomized, placebo controlled clinical trial. *Med Arh* 2012;66:198-200.
 106. Nasir A, Siddiqui MY, Mohsin M. Efficacy of Saboos-e-Asapghol (*Plantago ovata*) and Kalonji (*Nigella sativa*) in the Management of Hypertriglyceridemia. *IJPI* 2013;2:560-8.
 107. Mat MC, Mohamed AS, Hamid SS. Primary human monocyte differentiation regulated by *Nigella sativa* pressed oil. *Lipids Health Dis* 2011;10:1-11.
 108. Mahmood G, Bashir A, Murad S, Asghar J. Comparison of lipid lowering effects of *Nigella Sativa* and Gemfibrozil. *IJPRD* 2012;3:6-10.
 109. Moeen-Ud-Din H, Murad S, Fatima A. Placebo controlled study on Comparison of effects of *Nigella Sativa* and Nicotinic Acid along with Low Fat Diet and Physical Exercise on LDL-Cholesterol and HDL-Cholesterol. *Pak J Med Health Sci* 2014;8:306-9.
 110. Ahmad Alobaidi AH. Effect of *Nigella sativa* and *Allium sativum* coadministered with simvastatin in dyslipidemia patients: a prospective, randomized, double-blind trial. *Antiinflamm Antiallergy Agents Med Chem* 2014;13:68-74.