MINI-REVIEW ARTICLE

Nigella Sativa (Black Seeds), A Potential Herb for the Pharmacotherapeutic Management of Hypertension: A Review

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Abstract: Hypertension is one of the leading risk factors for stroke, myocardial infarction and unimpaired death. The prevalence of hypertension is extremely high among the global population, and many of them depend on modern medicines to manage their blood pressure. The modern antihypertensive medications include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, beta-adrenergic blockers, direct renin inhibitors, direct-acting vasodilators, alpha-adrenergic blockers and centrally acting drugs that are associated with many harmful and undesirable effects. The patients may consider traditional herbal medicines as a good strategy to manage chronic conditions due to the reasons such as perceived failure of allopathic medicines, relatively high cost of allopathic medicines, social-cultural practices and/or herbal knowledge, poor access to medical facilities and safety concerns about modern medicines. Nigella sativa (Black seeds) has been used to treat various conditions, including hypertension, obesity, diabetes, cancer, etc. Hence, the antihypertensive potential of N. sativa is analyzed in this review. The literature was searched in databases including Medline/PMC/PubMed, Google Scholar, ScienceDirect, Directory of Open Access Journals (DOAJ) and reference lists to identify articles associated with antihypertensive properties of N.sativa. Numerous randomized controlled trials and animal studies reported that N.sativa has potential antihypertensive effects. Hence, N. sativa could be used effectively to manage patients with stage 1 hypertension, and the patients using modern antihypertensive medications could reduce their doses by adding N. sativa into their regimen as adjuvant therapy.

Keywords: Nigella sativa, black seeds, kalonji, hypertension, thymoquinone, thymol, nigellone.

1. INTRODUCTION

Hypertension or high blood pressure is considered globally as an important risk factor for cardiovascular diseases, including myocardial infarction, stroke and premature death [1]. Blood pressure is the product of peripheral vascular resistance (PVR), and cardiac output (CO) is the product of stroke volume (SV) and heart rate (HR). Hence, the blood pressure could be modified by the factors affecting PVR, SV and/or HR [2]. Hypertension may occur due to various factors, including up-regulation of renin-angiotensin-aldosterone-system (RAAS), overactive sympathetic system, increased peripheral vascular resistance, psycho-emotional stress, oxidative stress, endothelial dysfunction, and some genetic factors [3].

The incidence of hypertension among the global population has been estimated as 972 million (26%) in 2000 [4] and 1.13 billion in 2015 [5]. Moreover, adults living in low and middle-income countries had more prevalence of hypertension (1.04 billion) than those from high-income countries (349 million) [6].

The modern antihypertensive medications include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, beta-adrenergic blockers, direct renin inhibitors, direct-acting vasodilators, alpha-adrenergic blockers and centrally acting drugs [7] and the first-line antihypertensive drugs include ACEIs, ARBs, CCBs, or thiazide diuretics as per the recommendation from the eighth joint national committee (JNC 8) and American college of cardiology/American heart association task force [8].

The use of herbal medicine to manage chronic conditions such as hypertension, diabetes, etc., is popular among the global population as modern medicines are associated with many harmful and undesirable side effects [9]. Moreover, the patients may consider traditional herbal medicines as a good strategy to manage chronic conditions due to the reasons such as perceived failure of allopathic medicines, relatively high cost of allopathic medicines, social-cultural practices and/or herbal knowledge, poor accessibility to medical facilities and safety concerns about allopathic medicines [10].

Nigella sativa (Black seeds or Black cumin seeds) is a miracle herb, and it has been used to treat various conditions, including hypertension, obesity, diabetes, cancer, etc [11]. Above all, Prophet Muhammad (PBUH) stated that “In
the black cumin, there is a cure for every illness except death” [12]. Hence, the antihypertensive potential of *N. sativa* is analyzed in this review. The major active constituents of *N. sativa* include thymoquinone (TQ), thymohydroquinone (THQ), dihydrothymoquinone, d-limonene, d-citronellol, p-cymene and 2-(2-methoxypropyl)-5-methyl-1,4-benzenedi-ol [13-15]. Moreover, it also contains alkaloids such as nigellidine, nigelicine, nigellicine, nigelicimine O-oxide and nigellone, along with other constituents [16-18].

The pharmacokinetics aspects of oral thymoquinone (the prominent active constituent of *N. sativa*) have been studied in animals, which revealed that the estimated clearance was 12.30 ± 0.30 ml/min/kg, the volume of distribution was 5,109.46 ± 196.08 ml/kg, the elimination half-life ($t_{1/2}$) was 274.61 ± 8.48 min and the protein binding was found to be 99% [19].

The acute toxicity study of *N. sativa* oil in mice determined that the lethal dose 50 (LD50) value for oral *N. sativa* oil was 28.8 ml/kg, and intraperitoneal *N. sativa* oil was 2.06 ml/kg. Moreover, the chronic toxicity study of *N. sativa* oil in rats revealed that the oral administration of 2 ml/kg of *N. sativa* oil for 12 weeks resulted in stability of key hepatic enzymes and integrity of organs. Hence, the use of *N. sativa* is considered safe as it has very high LD50 values and no chronic toxicity potentials [20].

This review article provides justification/information to use of *N. sativa* seed for hypertension along with conventional antihypertensive medications from the evidence of various clinical studies.

2. METHODS

The literature was searched in databases including Medline/PMC/PubMed, Google Scholar, sciencedirect, Directory of Open Access Journals (DOAJ) and reference lists in this review, using keywords such as hypertension, high blood pressure, *Nigella sativa*, black seeds, black cumin seeds, and kalonji. The publications written in the English language were included in this review, while the duplicate publications were excluded.

3. RESULTS AND DISCUSSION

Numerous randomized controlled clinical trials (RCTs) have been performed to observe the antihypertensive effects of *N. sativa* Table (1). A significant reduction of blood pressure was noticed almost in every patient who participated in those RCTs, which indicate that the stage 1 hypertension could be managed effectively using *N. sativa*, and the patients using allopathic antihypertensive medications could reduce the incidence of undesirable effects by decreasing their doses through the addition of *N. sativa* into their regimen as adjuvant therapy.

A randomized, double-blind, placebo-controlled clinical trial accomplished through Dehkordi FR et al. reported a significant reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a dose-dependent manner in individuals with mild hypertension who were supplemented with 100 and 200 mg of *N. sativa* extract two times daily for 8 weeks. In addition, the administration of *N. sativa* extract also resulted in a significant reduction of low-density- lipid-protein (LDL)-cholesterol, and the study did no longer find any complications, which imply more secure use of *N. sativa* to treat sufferers of high blood pressure [21] and another randomized, double-blind, placebo-controlled clinical trial of 123 patients, reported a favorable impact of capsules containing powdered *N. sativa* seeds on blood pressure along with fasting blood glucose (FBG), serum lipids, body-mass index (BMI), waist-hip ratio, serum alanine aminotransferase (ALT) and serum creatinine [22].

Similarly, a double-blind, placebo-controlled trial of central obese men revealed that the supplementation of *N. sativa* leads to a significant decline in SBP, body weight, and waist circumference [23] and a clinical study of patients receiving drugs such as atenolol 50 mg once a day, metformin 500 mg twice daily, simvastatin 10 mg once a day, and clopidogrel 75 mg once daily demonstrated that the adjuvant therapy of 250 mg twice daily of *N. sativa* for 6 weeks resulted in improvement in blood pressure, waist circumference, fasting blood sugar, LDL, HDL and triglycerides compared to the standard group [24].

Table 1. Clinical studies supporting the use of *N. sativa* to manage hypertension.

| S.No | Type of Study | Findings |
|------|--------------|----------|
| 1 | Randomized, double-blind, placebo-controlled clinical trial [21] | Significant reduction of SBP, DBP, and LDL-cholesterol. |
| 2 | Randomized, double-blind, placebo-controlled clinical trial [22] | Improvement in BP, FBG, serum lipids, BMI, waist-hip ratio, ALT and creatinine. |
| 3 | Randomized, double-blind, placebo-controlled clinical trial [23] | Significant decline in SBP, body weight, and waist circumference. |
| 4 | Clinical study [24] | Improvement in BP, FBG, waist circumference, LDL, HDL and triglycerides. |
| 5 | Open labeled study [25] | Significant improvement in SBP, DBP, LDL. |
| 6 | Randomized, double-blind, placebo-controlled clinical trial [26] | Significant decrease in SBP, and DBP. |
| 7 | Randomized, double-blind, placebo-controlled clinical trial [27] | Significant lowering of SBP and significant increase in HDL. |
| 8 | Single-blind, nonrandomized controlled clinical trial [28] | Significant reduction of SBP, DBP, MAP, TC, LDL, TC/HDL, LDL/HDL and significant elevation of HDL. |
| 9 | Randomized, double-blind, controlled clinical trial [29] | Slight decrease in SBP and DBP. |
An open-labeled study of 90 patients with metabolic syndrome reported a significant improvement in systolic blood pressure, diastolic blood pressure and low-density-lipoprotein (LDL)-cholesterol by the administration of *N. sativa* for 8 weeks [25].

Fallah Huseini H *et al.* carried out a randomized, double-blind, placebo-controlled clinical trial of 70 healthy volunteers who received 5 ml of *N. sativa* oil, observed a significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP). However, the study did not find any significant modifications in different parameters including body mass index and blood levels of creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase [26] and a randomized, double-blind, placebo-controlled clinical trial of 20 patients of stage 1 hypertension and who received 1000 mg of powdered *N. sativa* seeds 2 times daily for 50 days, revealed that there was a significant lowering of systolic blood pressure (SBP) in *N. sativa* treated group. It has also been stated that *N. sativa* treated group shown a significant increase in high-density-lipoprotein (HDL)-cholesterol [27].

A single-blind, nonrandomized controlled trial of 57 patients with type 2 diabetes demonstrated that 2 g daily supplementation of *N. sativa* for 1 year resulted in a significant reduction of systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate along with a significant elevation of high-density-lipoprotein (HDL)-cholesterol [27].

3.1. Proposed Mechanisms of Antihypertensive Activity of *N. Sativa*

*N. Sativa* may decrease the blood pressure probably through remarkable mechanisms (Fig. 1), which include calcium channel blockade, diuretic activity, angiotensin-converting enzyme (ACE) inhibition, increased cardiac heme oxygenase-1 activity, prevention of loss of plasma nitric oxide, antioxidant activity, and cardiac depressant activity, as proposed by diverse studies.

3.1.1. Calcium Channel Blockade

Calcium channel blockade leads to the prevention of entry of (Ca$^{2+}$) ions into the vascular smooth muscle ensuing in decreased intracellular Ca$^{2+}$ concentrations, diminished formation of calcium-calmodulin (Ca-CAM) complex, and declined vascular resistance, ultimately leading to vasodilation and decreased blood pressure [30].

A study by Magyar J *et al.* demonstrated that thymol of *N. Sativa* inhibits the L-type calcium (Ca$^{2+}$) ion channels ensuing in inhibition of Ca$^{2+}$ release from sarcoplasmic reticulum leading to vasodilation and reduction of blood pressure [31], and it has been reported that the calcium (Ca$^{2+}$) ion channels might also be inhibited by nigellone of *N. Sativa* [32].

In addition, the treatment of isolated rat aorta with *N. Sativa* oil leads to dose-dependent vasodilation probably through the blockade of voltage-sensitive and receptor-operated calcium channels [33] and Jaarin K *et al.* demonstrated that the administration of *N. sativa* oil for 8 weeks in L-NAME induced hypertensive rats, lead to a reduction of blood pressure via calcium channel blockade which is comparable to that of nicardipine, a dihydropyridine calcium channel blocker coupled with antioxidant effects [34]. Moreover, the simultaneous administration of *N. sativa* and amloidipine produced better blood pressure control in hypertensive rats [35].

![Fig. (1). Probable antihypertensive mechanisms of *N. sativa.*](image-url)

3.1.2. Diuretic Activity

Diuretics enhance the urinary excretion of water and electrolytes, leading to a reduction of blood volume ensuing in decreased stroke volume, cardiac output and blood pressure [36].

*N. sativa* may lessen the blood pressure via its diuretic activity as it was reported by Zaoui A *et al.* The administration of 0.6 mL/kg of *N. sativa* extract in spontaneously hypertensive rats, for 15 days resulted in increased urinary excretion of electrolytes such as Na$^+$, K$^+$, Cl$^-$, and urea [37]. It has additionally been demonstrated by Zeggwag NA *et al.* that *N. sativa* accelerated the urinary excretion of electrolytes and glomerular filtration rate (GFR) [38].

3.1.3. Angiotensin-converting Enzyme (ACE) Inhibition

Angiotensin-converting enzyme (ACE) is involved in the conversion of angiotensin I to angiotensin II, which will increase the blood pressure through vasoconstriction and the release of aldosterone [39]. Hence, inhibition of the angiotensin-converting enzyme (ACE) would result in de-
increased formation of angiotensin II, leading to a reduction of blood pressure.

Jaarin K. et al. demonstrated that the administration of *N. sativa* oil leads to the inhibition of the angiotensin-converting enzyme (ACE) and reduction of blood pressure, in L-NAME-induced hypertensive rats [34]. In addition, intraperitoneal injection of hydroalcoholic extract of *N. sativa* and its active constituent, thymoquinone antagonized the elevated systolic blood pressure and mean arterial pressure in angiotensin II-induced hypertensive rats [40], and the concurrent administration of *N. sativa* and losartan produced a more prominent reduction of blood pressure. It has been suggested that the dosage adjustment of losartan is possible while *N. sativa* is used as adjuvant therapy [41].

### 3.1.4. Reduction of Oxidative Stress

Oxidative stress could impair vasodilation and increase blood pressure by reducing the synthesis or release of nitric oxide (NO) and inducing the endothelial dysfunction ensuing in vascular smooth muscle cells proliferation and deposition of collagen, leading to thickening of the tunica media and narrowing of the vascular lumen [42].

Various randomized controlled clinical trials (RCTs) confirmed that *N. sativa* exerts potential antioxidant properties through the elevation of levels of superoxide dismutase (SOD) [43], glutathione [44], total antioxidant capacity [45], and erythrocyte glutathione peroxidase (GSH-Px) and reduction of plasma levels of malondialdehyde (MDA) [46].

Moreover, Khattab M et al. demonstrated that the supplementation of thymoquinone of *N. sativa* produced an antihypertensive effect through the inhibition of production of superoxide radical, in nitric oxide (NO) deficient hypertensive rats [47]. Sayed HM et al. reported that the administration of *N. sativa* produced antihypertensive effect through antioxidant effects in L-NAME-induced hypertensive rats [48].

In addition, Jaarin K et al. demonstrated that the administration of *N. sativa* oil for 8 weeks in L-NAME induced hypertensive rats, leads to increased cardiac heme oxygenase-1 (HO-1) activity, which in turn reduces angiotensin II-induced inflammation and NADPH oxidase-mediated oxidative stress resulting in attenuation of blood pressure. They have also reported that *N. sativa* oil supplementation may prevent the loss of plasma nitric oxide (NO) [34].

### Table 2. Proposed mechanisms of Antihypertensive activity of *N. sativa*.

| S.No | Proposed Mechanism                  | Authors                  | Findings                                                                                           |
|------|------------------------------------|--------------------------|----------------------------------------------------------------------------------------------------|
| 1    | Calcium channel blockade           | Magyar J et al. [31]     | Thymol of *N. Sativa* inhibits the L-type calcium (Ca$^{2+}$) ion channels ensuing in inhibition of Ca$^{2+}$ release from sarcoplasmic reticulum leading to vasodilation and reduction of blood pressure. |
| 2    | Calcium channel blockade           | Salem ML [32]            | Nigellone of *N. Sativa* may also inhibit the calcium (Ca$^{2+}$) ion channels.                    |
| 3    | Calcium channel blockade           | Cherkaoui-Tangi K et al. [33] | Treatment of isolated rat aorta with *N. Sativa* oil leads to dose-dependent vasodilation, probably through the blockade of voltage-sensitive and receptor-operated calcium channels. |
| 4    | Calcium channel blockade           | Jaarin K et al. [34]     | Reduction of blood pressure *via* calcium channel blockade is comparable to that of nifedipine in L-NAME induced hypertensive rats. |
| 5    | Calcium channel blockade           | Alam MA et al. [35]      | Simultaneous administration of *N. sativa* and amlodipine produced better blood pressure control in hypertensive rats. |
| 6    | Diuretic activity                  | Zaoui A et al. [37]      | Increased urinary excretion of electrolytes, such as Na⁺, K⁺, Cl⁻ and urea.                         |
| 7    | Diuretic activity                  | Zeggwagh NA et al. [38]  | Accelerated urinary excretion of electrolytes and glomerular filtration rate (GFR).               |
| 8    | Angiotensin-converting enzyme (ACE) inhibition | Jaarin K et al. [34] | Inhibition of angiotensin-converting enzyme (ACE) and reduction of blood pressure, in L-NAME-induced hypertensive rats. |
| 9    | Angiotensin-converting enzyme (ACE) inhibition | Enayatifard L et al. [40] | Antagonized effect of elevation of SBP and MAP in angiotensin II-induced hypertensive rats.          |
| 10   | Angiotensin-converting enzyme (ACE) inhibition | Ahad A et al. [41] | Concurrent administration of *N. sativa* and losartan produced more prominent reduction of blood pressure. |
| 11   | Reduction of oxidative stress      | Khattab M et al. [46]    | Inhibition of the production of superoxide radical, in nitric oxide (NO) deficient hypertensive rats. |
| 12   | Reduction of oxidative stress      | Sayed HM et al. [47]     | Antioxidant effects in L-NAME-induced hypertensive rats.                                          |
| 13   | Increased cardiac heme oxygenase-1 (HO-1) activity | Jaarin K et al. [34] | Increased cardiac heme oxygenase-1 (HO-1) activity leads to a reduction of angiotensin II-induced inflammation and NADPH oxidase-mediated oxidative stress resulting in attenuation of blood pressure in L-NAME induced hypertensive rats. |
| 14   | Prevention of loss of plasma nitric oxide (NO) | Jaarin K et al. [34] | *N. sativa* oil supplementation may prevent the loss of plasma nitric oxide (NO).                   |
| 15   | Cardiac depressant activity        | El Tahir KE et al. [48]  | Decreased blood pressure probably through the reduction of heart rate and myocardial contractility *via* central mechanism. |
3.1.5. Cardiac Depressant Activity

El Tahir KE et al. performed a study and suggested that the administration of N. sativa decreased the blood pressure probably through the reduction of heart rate and myocardial contractility via central mechanism [48]. We summarized here proposed mechanisms of antihypertensive activities of N. sativa from the reported studies Table (2).

3.2. Drug Interaction Potentials of N. sativa

Interference of the effects of one drug by the coadministered drug(s), herb, food, alcohol or other substances, is termed drug interaction [49, 50]. Furthermore, the drug interaction ensuing in enhanced toxic effects or diminished therapeutic efficacy is known as adverse drug interaction, which is considered as preventable medication error [51]. The patients with hypertension may take one or more modern antihypertensive medications, which include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, beta-adrenergic blockers, direct renin inhibitors, direct-acting vasodilators, alpha-adrenergic blockers and centrally acting drugs [7].

N. sativa may interact pharmacokinetically with concomitantly administered drugs as the extracts of N. sativa have shown inhibition of cytochrome P-150 (CYP) 3A4/5/7, 2C9 mediated metabolism of substrates in in-vitro studies [52]. In addition, N. sativa could interact pharmacodynamically with modern antihypertensive medications as it has reasonable antihypertensive efficacy. The interaction of N. sativa with modern antihypertensive medications would be beneficial as this interaction would help to reduce the doses of modern antihypertensive medications.

An animal study demonstrated that the administration of a combination of N. sativa and losartan (an ARB) ensued in a more prominent reduction of systolic blood pressure compared to N. sativa alone [41]. Hence, the authors suggested adjusting the dose of losartan when N. sativa and losartan were used concomitantly.

CONCLUSION

Numerous randomized controlled clinical trials (RCTs) have reported that N. sativa has potential antihypertensive activity and various animal studies proposed that N. Sativa could decrease blood pressure through remarkable mechanisms, which include calcium channel blockade, diuretic activity, angiotensin-converting enzyme (ACE) inhibition, increased cardiac heme oxygenase-1 activity, prevention of loss of plasma nitric oxide, antioxidant activity, and cardiac depressant activity. Moreover, the active constituents of N. sativa, such as thymol, and nigellone, have been identified as potential antihypertensives.

A significant reduction of blood pressure was noticed almost in every patient who received N. sativa, which indicate that stage 1 hypertension could be managed effectively using N. sativa and the patients using conventional antihypertensive medications could add N. sativa into their regimen as an adjuvant therapy, which may help to reduce the adverse effects of conventional medicines through the reduction of their doses.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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