Pharmacological Activity of Nigella Sativa: A Review


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ABSTRACT

*Nigella sativa* (NS) are dark, thin, and crescent-shaped, seeded shrub belonging to the family Ranunculaceae, commonly growing on Mediterranean coasts in Saudi Arabia, northern Africa and Asia. It is a widely used medicinal plant throughout the world. It contains many active components including nigellicine, nigellimine, nigellidine and alphahederin, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol. It was reported to possess numerous pharmacological effects related to several organs of the body. It is clear that most of the potent and fruitful activity resides in its volatile oil and a protein component. However, the volatile oil suffers the drawback of the bronchoconstricting effect of thymoquinone. The positive roles of Nigella sativa (NS) has been suggested to have antioxidants on brain development and learning and memory and neuroprotective effects. It has been recommended for using on regular basis in Tibb-e-Nabwi (Prophetic Medicine). It has been widely used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal. Extensive studies on *N. sativa* have been carried out a wide spectrum of its pharmacological actions which may include antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmylytic, bronchodilator.

Key words: Black Cumin, Nigellicine, *Nigella sativa*, pharmacology

INTRODUCTION

Kalonji (*Nigella sativa*) is a dicotyledonous of ranunculacea is an amazing herb with a religious background and commonly grows in the Eastern Europe, Middle East, and Western Asia. The seeds of *N. sativa* are the source of the active ingredient of this plant [1]. It is a black seed referred by Prophet Mohammed as a panacea (universal healer), that is a remedy for all ailments but cannot prevent ageing or death [2]. The use of black seeds has been mentioned in various religious and ethnic books. Black seeds are identified as the curative black cumin in the holy bible. In the Unani-Tibb system of medicine which originate from Hippocrates, his contemporary Galen and Ibn- sina has regarded black seed as a valuable remedy in the hepatic and digestive disorder. Through thousands of years, until the time being, millions of people in the mediterranean region and Far East countries use the oil of *N. sativa* seeds daily as a natural protective and curative remedy. Several active compound have been isolated from *N. sativa* seed and its oil including thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine and alpha-hederin. [3,4]. It has been recorded that *N. sativa* seeds were prescribed by ancient Egyptian and Greek physicians to treat headache, nasal congestion, toothache and intestinal worm, as well as a diuretic to promote menstruation and milk production[5]. In Ayurvedic system of medicine, the seeds are given with butter-milk to obstinate hiccups and are also used in loss of appetite, vomiting, dropsy. They are also used as emmenagogue and galactogogue. The seed oil and oil of *N. sativa* were frequently used in ancient remedies (Unani, Ayurveda, Chinese and Arabic) in Asian countries and in the middle east [6, 7].

In different combinations, the seeds of *N. sativa* have been used in obesity and dyspnoea. *N. sativa* and its ingredients are used in immune-stimulatory, anti-inflammatory, hypoglycemic, antihypertensive, antiasthmatic, antimicrobial, antiparasitic, antioxidant and anticancer effects [8, 9]. They have antibilious property and are administered internally in intermittent fever. It is used as a inhalation of dried seeds releases cold. The objective of this article is to review the reported dermatological effects of *N. sativa*. The seeds have also been used in mercury poisoning, and leprosy [10].

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**Chemical constituents:** *Nigella sativa* seeds contain 36 to 28% fixed oil, proteins, alkaloid, saponin and 0.4 to 2.5% essential oil. It is composed of unsaturated fatty acid that includes arachidonic, eicosadienoic, linoleic and linolenic acid. The saturated fatty acid present in the oil are palmitic, stearic and myristic acid [11]. Many components were characterized but the pharmaco-gically active constituent of volatile oil are thymoquinone, dithymoquinone, thymol and thymohydroquinone [12, 13]. The crystalline active principle, nigellone is the only constituent of the carbonyl fraction of the oil. Four alkaloids have been reported as constituent of *Nigella Sativa* seeds. Nigellicine, nigellidine, nigellimine [14, 15, 16]. Recently, a triterpene saponin Alfa herein was isolated from the seeds of *Nigella sativa*. α-heredin is known to have antitumor activity[17]. Triglycoside quercetin 3-glucoside, kaempferol 3-glucoside and rutin were also isolated from the seeds of *Nigella sativa*. *Nigella sativa* seeds contain other ingredient including nutritional components such as carbohydrates, fats vitamins mineral elements and proteins including eight or nine essential amino acid. [18]. Monosaccharide in the form of glucose rhamnose, xylose and arabinose are also found. The seeds also contain carotene, which is converted by liver to vitamin A, the *Nigella sativa* seeds are also a source of calcium, irons and potassium [19].

**PHARMACOLOGICAL ACTIVITIES**

**Antidiabetic activity:** Studied that effect of the *Nigella Sativa* have glucose lowering effect in rats. Further study on the plant mixture containing *N. sativa* revealed that the blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis and the plant extract mixture may prove to be useful therapeutic agent in the treatment of non-insulin dependent diabetes mellitus [20, 21]. The volatile oil of *N. sativa* alone also produced a significant hypoglycemic effect on normal and alloxan induced diabetic rabbits without changes in insulin levels [22]. The clinical study of *N. sativa* improvement with reference to total cholesterol, low density lipoprotein
cholesterol, and fasting blood glucose indicating effective as an add-on therapy in patients of insulin resistance syndrome [23].

Anticancer activity: Studied that anticancer activity of N. sativa was have the natural killer (NK) cell activity was observed in advanced cancer patients receiving multimodality immunotherapy program [24]. In another study, antineoplastic activity of thymoquinone was investigated using mouse keratinocytes, papilloma (SP-1) and spindle-17 carcinoma cells. In SP-1 cells thymoquinone induced G0/G1 cell-cycle arrest, these have a potential role for thymoquinone as a chemopreventive agent, particularly at the early stages of skin tumorigenesis [25]. Antitumor activity of thymoquinone and thymohydroquinone was also demonstrated using tumor cell lines and fibrosarcoma, and murine and squamous cell carcinoma [26]. In a mouse xeno-graft model, a combination of thymoquinone and diosgenin significantly reduced tumor volume, mass and increased apoptosis [27].

Using an in vitro cell migration assay, it was found that, thymoquinone inhibited the migration of both human and mouse melanoma cells. The inhibition of metastasis by thymoquinone was also observed in vivo in B16F10 mouse melanoma model and was accompanied by a decrease in expression of NLRP3 inflammasome which resulted in decreased proteolytic cleavage of caspase-1 The authors suggested that, thymoquinone(TQ) can be a potential immunotherapeutic agent not only as an adjuvant therapy for melanoma, but also, in the control and prevention of metastatic melanoma [28].The chemo-sensitizing effect of TQ and 5-fluorouracil (5-FU) on gastric cancer cells both in vitro and in vivo is reported by Lei et al. Pretreatment with TQ significantly increased the apoptotic effects induced by 5-FU in gastric cancer cell lines in vitro. Further, the combined treatment of TQ with 5-FU represents a significantly more effective antitumor agent than either agent alone in a xenograft tumor mouse model [29].

Cardiovascular activity: Studied that Nigella sativa and its active constituent thymoquinone on the arterial blood pressure and heart of anaesthetized rats. Both agents produce a dose dependent decrease in the arterial blood processor and heart rates. These effects were significantly antago-nized by atropine, mainly via the involvement of 5-hydroxy tryptaminergic and muscarinic mechanism. These findings were significantly comparable with the standard anti-hypertensive drug nifedipine[30]. The effect of the drug was concluded to be partially due to its diuretic effect which was comparable to furosemide. In another study, Nigella sativa extract to normal rats has shown a homogenous cardiac hypertrophy and enhanced cardiac contractility at baseline conditions. The hearts of Nigella-treated rats developed a moderate but significant hypertrophy that was evident by an increase in the heart weight to body weight ratio. The observed Nigella-induced cardiac hypertrophy was associated with an increase in the baseline cardiac inotropic properties [31].

Hepato-protective activity: It is reported that Nigella sativa administration protects hepatic tissue from deleterious effects of toxic metals such as lead, and attenuates hepatic lipid peroxidation following exposure to chemicals such as carbon tetrachloride [32]. Hepatotoxicity is associated with alteration in the levels and activities of certain enzymes such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), oxidant scavenger enzymes system including glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT). The protective action of thymoquinone against the hepatotoxin: tertbutyl hydperoxide has been demonstrated using isolated rat hepatocytes [33].

Neuro-pharmacolgical activities: The aqueous and methanol extracts of defatted Nigella sativa seeds were shown to possess a potent central nervous system, especially depressant action in the case of the methanolic extract [34]. An anxiolytic drug acts by increasing the 5-HT and decreasing the 5-HIAA levels in brain. A long term administration of Nigella sativa increases 5-HT levels in brain and improves learning and memory in rats [35]. Neuprotective effects of Aqueous and hydroalcoholic extracts of Nigella sativa were evaluated for their neuroprotective effects on middle cerebral artery occluded (MCAO) rats. Locomotor activity and grip strength of animals were improved in both aqueous and hydroalcoholic extracts pretreated rats. Pretreatment of Nigella sativa extracts show the reduction in TBARS, elevation in glutathione, SOD and CAT levels as compared with MCAO rats. The neuroprotective effects of both the extracts of Nigella sativa in cerebral ischemia were observed. The neuroprotective effects could be due to its antioxidant, free radical scavenging, and anti-inflammatory properties [36].

Gastro-protective activity: The anti-ulcer potential of Nigella sativa aqueous suspension on experimentally induced gastric ulcers and basal gastric secretion in rats was examined to rationalize its use by herbal and Unani medicine practitioners. Acute gastric ulceration was produced by various
noxious chemicals in Wistar albino rats. Anti-secretory studies were undertaken in a separate group of rats. Gastric wall mucus contents and non-protein sulfhydryl concentration were estimated, and gastric tissue was examined histopathologically. The anti-ulcer effect of *N. sativa* is possibly prostaglandin-mediated and/or through its antioxidant and anti-secretory activities [37].

**Antibacterial activity:** The crude extracts of *Nigella sativa* were tested for antimicrobial effectiveness against different bacterial isolates which comprised of 16 gram negative and 6 gram positive representatives. These isolate was showed multiple resistances against antibiotics, especially the gram negative ones. Crude extracts of *Nigella sativa* showed a potential effect against some of the test organisms. The most valuable extracts were the crude alkaloid and water extracts. Gram negative isolates were affected more than the gram positive ones [38].

**Immunomodulatory activity:** Studied that immunomodulating and cytotoxic properties of volatile oil of *N. sativa* seeds was investigated in a Long-Evans rat model designed to examine the effect of *N. sativa* seeds on selected immune components. Long-Evans rats were challenged with a specific antigen (typhoid TH) and treated with *N. sativa* seeds; Treatment with *N. sativa* oil induced about 2-fold decrease in the antibody production in response to typhoid vaccination as compared to the control rats but there was a significant decrease in splenocytes and neutrophils counts, but a rise in peripheral lymphocytes and monocytes in the these animals. These results indicated that the *N. sativa* seeds could be considered as a potential immunosuppressive cytotoxic agent [39].

**Anticonvulsant activity:** Studied that *N. sativa* seed effectively against PTZ-induced convulsions. The antiepileptic activity of the volatile oil in this model maybe attributed mainly to its content of TQ and p-cymene and to a lesser extent, α-pinene. Volatile oil and its component p-cymene effectively suppressed convulsions induced by MES [40]. The antiepileptic effect of curcumin and *N. sativa* oil in the pilocarpine model of epilepsy in comparison with valproate was evaluate. Treatment of pilocarpinized rats with curcumin and valproate ameliorated most of the changes in amino acid concentrations and reduced the histopathological abnormalities induced by pilocarpine, while *N. sativa* oil failed to improve the pilocarpine-induced abnormalities [41].

**Antifungal activity:** The methanolic extracts of *N. sativa* have the strongest antifungal effect against different strains of *Candida albicans*. An intravenous inoculum of *Candida albicans* produced colonies of the organism in the liver, spleen and kidneys. Treatment of mice with the plant extract 24 h after the inoculation caused a considerable inhibitory effect on the growth of the organism in all organs studied. It was reported that the aqueous extract of *N. sativa* seeds exhibits inhibitory effect against candidiasis in mice [42]. Two novel antifungal defensins named Ns-D1 and Ns-D2, were isolated from seeds of *N. sativa* and sequenced. The Ns-D1 and Ns-D2 defensins displayed strong divergent antifungal activity towards a number of phytopathogenic fungi [43].

**Anti-histaminic/anti allergic properties of *N. sativa*:** Histamine is released by basophils and mast cells, producing allergic reactions associated with bronchial asthma, urticaria and food allergy. Increased numbers of mast cells are associated with gastric mucosal damage induced by the use of NSAID [44]. The use of NS seeds and its active ingredients has a considerable effect on the histamine mediated inflammatory and gastric diseases. A low concentration of nigellone effectively inhibits histamine release from mast cells have shown that volatile oil therapy of NS and more so its constituent TQ, significantly reduced mast cell number and the gastric ulcerated lesions in ethanol treated rats [45]. Low concentration of nigellone effectively inhibits the histamine release from the mast cells, indicating an anti-asthmatic role. TQ dimer isolated from NS’s volatile oil, ‘Nigellone’ suppressed symptoms when given orally to bronchial asthma patients with effective results without any toxicity [46]. Administration of *N. sativa* oil to patients with allergic problems, like allergic rhinitis, atopic eczema, and bronchial asthma decreased the immunoglobulin E, and eosinophil count [47].

**Anti-inflammatory properties:** Interventions in pathways of inflammation have been known to possibly delay cancer development and progression thereby improving patient life quality. Compounds like PGs and leukotrienes (LT) are well known as inflammatory mediators [48, 49]. It competitively inhibit the pro-inflammatory cytokines and tumor necrosis factor a [50]. Oral doses of PUFAs have been shown to exhibit bacteriostatic effects on H. pylori, though higher doses could prove bactericidal [51, 52, 53]. It a powerful anti-inflammatory compound by inhibiting the synthesis of inflammatory cytokines [54, 55]. Namely leukotrienes and thromboxanes by inhibiting the lipoxygenase (LOX) and cyclooxygenase (COX) activities [56]. The inflammatory LOX cascade
plays a vital role in the gastric ulcers induced by irritants such as alcohol [57]. Therefore, inhibition of 5-LOX enzyme could well be an approach toward apoptosis [58]. The anti-allergic effects of N. sativa components could be attributed to allergic rhinitis. Moreover, N. sativa should be considered for treating allergic rhinitis when the effects of other anti-allergic drugs need to be avoided [59].

**Anti-microbial effects of N. sativa on gastric ulcers:** Studied that Nigella sativa seed extract has been shown to possess anti-microbial activity against Staphylococcus aureus, Escherichia coli, Proteus vulgaris, and Candida albicans. Its essential oils act more against gram-positive bacteria than the gram-negative ones. Nigella sativa essential oil has a higher antibacterial activity compared to tetracycline, cefuroxime, and ciprofloxacin and stronger antifungal properties in contrast to clotrimazole [60]. Though antimicrobial agents could successfully remove H. pylori infection it could also lead to regression of disorders associated with H. pylori. H. pylori is increasingly turning antibiotic resistant, making it necessary to research out novel effective agents. Nigella sativa possesses in vitro antihelicobacter activity comparable to triple therapy [61]. In an in vitro experiment, Nigella sativa extract produced a 100% growth inhibition of all the H. pylori strains that were tested within 60 min [62].

**Antiviral:** Studied that Nigella sativa was found to enhance helper T cell (T4) and suppressor T cell (T8) ratio and increased natural killer (NK) cell activity in healthy volunteers [63]. Besides improvement in immunity, Nigella sativa extract have some inhibitory effect on the human immune deficiency virus protease but the active principle(s) responsible for this activity was not identified [64].

**Antioxidant activity:** Studied that methanol extracts of Nigella sativa have strong antioxidant activity using the oxygen radical absorbance capacity method and a cell-based assay [65]. Thymoquinone has been shown to suppress the Fe-NTA-induced oxidative stress, hyperproliferative response and renal carcinogenesis in Wistar rats [66]. It was suggested that dietary supplementation of black seeds powder inhibits the oxidative stress caused by oxidized corn oil in rats [67]. The modulatory effect of Thymoquinone on erythrocyte lipid peroxidation and antioxidant status during 1,2-dimethylhydrazine- (DMH-) induced colon carcinogenesis after initiation in male Wistar rats was investigated [68].

**Antiparasitic:** Studied that Alcoholic extract of Nigella sativa seeds was applied daily for 15 weeks to cutaneous leishmaniasis produced experimentally in mice by a subcutaneous inoculation of Leishmania major at the dorsal base of the tail. The morphology of the lesion and the body weight of mice were monitored daily. There was no significant difference between the average weight of mice receiving Nigella sativa extract ointment and controls but the lesion diameter and symptoms of inflammation were significantly lesser in the test group as compared to the controls [69]. Nigella sativa seed was tested against miracidia, cercariae and adult worms of Schistosoma mansoni and showed strong biocidal activity against all stages of the parasite, as well as an inhibitory effect on egg-laying of adult female worms, indicating an antischistosomal potential of the Nigella sativa [70].

**Contraceptive and anti-fertility activity:** Studied that ethanolic extract of N. sativa seeds was found to possess an anti-fertility activity in male rats which might be due to inherent estrogenic activity of Nigella sativa [71].

**Nephroprotective activity:** Nephro-protective effect of vitamin C and Nigella sativa oil was observed against gentamicin (GM) associated nephrotoxicity in rabbits. Serum creatinine, blood urea nitrogen, and antioxidant activity were measured as indicators of nephrotoxicity for all the groups of rabbits. It was revealed that vitamin C and Nigella sativa oil both had nephroprotective effect as they lowered the values of serum creatinine, blood urea nitrogen, and antioxidant activity as compared to GM control group values. When these two antioxidants were given as combination, they proved to have synergistic nephroprotective effect [72].

**Anti-asthmatic effects:** The effect of nigellone and Thymoquinone on trachea (antispasmodic effect) and their influence on respiratory clearance. The effects on Ba²⁺ carbachol- and leukotriene-induced trachea contractions and the transport of the fluorescence dye rhodamin B concerning ciliary action in the tracheal area were investigated using a micro dialysis technique. Nigellone and high concentrations of Thymoquinone had a concentration-dependent inhibitory effect on the trachea when being contracted by the depolarizing effect of Ba²⁺. The trachea contractions induced by leukotriene-d (4) LT4 were inhibited by nigellone and by Thymoquinone. It was concluded that nigellone possesses an antispasmodic effect and an increase in mucociliary clearance but Thymoquinone do not have such effects. Therefore, it is suggested that nigellone but not Thymoquinone may be useful in treatment of different respiratory diseases [73].
Toxicological studies: Studied that the seeds of Nigella sativa extract and its constituent appear to have a low level of toxicity. In a recent study of diazinon induced organ toxicity, with Nigella sativa seeds extract given orally for three and six weeks, the study observed attenuated extensive changes of hematological and biochemical parameters in diazinon-treated rats. Some other studies also demonstrate that treatment with Nigella sativa resulted in significant decrease of haematological disorders induced by aflatoxin [74]. There is no remarkable pathological changes were recorded in bone marrow of animals treated with suspension of Nigella sativa in carbon tetrachloride induced bone marrow toxicity [75].

REFERENCES


70. Mohamed AM, Metwally NM, Mahmoud SS. Nigella sativa seeds against Schistosoma mansoni different stages. Mem. Inst. Oswaldo Cruz 2005; 100: (2), 205–211.


