



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article


December 2020 Vol.:20, Issue:1

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A Review on Scientific Researches and Pharmacological Potential of *Nigella sativa* (Black Cumin Seed)



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

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Submitted: 01 November 2020
Revised: 20 November 2020
Accepted: 10 December 2020



HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: *Nigella sativa*; Black Cumin; Black Seeds; Antiviral; COVID-19

ABSTRACT

Nigella sativa or black cumin belongs to Ranunculaceae botanical family and is widely used as a medicinal herb throughout the world. The *Nigella sativa* seed and its oil have been useful in the treatment of different ailments. The black seeds have many acclaimed medicinal properties such as hypotensive, antiviral, antifungal, etc. Numerous pharmacological properties of black cumin seeds have been investigated by researchers in the past few decades. This review is proposed to enlighten the pharmacological properties of *Nigella sativa* as varied studies like randomized controlled trials, case studies, pilot studies, and *invitro* and *in-vivo* studies have confirmed that it possesses antiviral, antioxidant, immunomodulatory, bronchodilatory, anti-inflammatory, anticoagulant, antihistaminic, antitussive, antipyretic and analgesic activities.

INTRODUCTION:

The *Nigella sativa* seed and its oil have an old history of traditional usage in the Indian and Arabian culture as food and medicine and have been used in the treatment of different health conditions of the digestive tract, respiratory system, kidney and liver functions, cardiovascular system, and immune system support. Studies reveal that the major bioactive principal constituent of *N. sativa* is Thymoquinone with a range of therapeutic benefits including antioxidant, anti-inflammatory, anti-cancer, antibacterial, antifungal activity, and anticonvulsant activity. Immunomodulatory effects of *N. sativa* have also been reported. Also, several investigations reported the antiviral effect of the black seed. Lately, a molecular docking-based study identified α -hederin and nigellidine among the compounds of *N. sativa* as novel inhibitors of SARS-CoV-2. Also, the folklore practice of taking black seed and its steam has been found to relieve the symptoms of the ailment. To gain further understanding of the therapeutic benefits, we revisited the pharmacological potentials of *N. sativa* seed and its bioactive, and present a comprehensive outline on the prospects of these natural products for the prevention and cure of different diseases. [1,2,3].

NAMES OF THE BLACK SEED:

Common name: Black seed

Scientific name: *Nigella sativa*

Urdu: Kalonji

Arabic: Habba-tu sawda/ Habba Al-Barakah

English: Black cumin/ Black seed

Persian: Shonaiz

Bengali: Kalajira

Hindi/Nepali: Mangrail

Nigella sativa Linn:

Nigella sativa L. is a small bush plant ranging 20-90 cm in length listed in the botanical family, Ranunculaceae, home-grown in countries as Southern Europe, North Africa, and Southeast Asia; cultivated in many regions of India, Pakistan, Saudi Arabia, Turkey, etc.

Leaves of the plant are tapering green and rosaceous flowers of varied colors like yellow, pink, white, pale blue, or purple with 5-10 petals. numerous tiny, dark black in color seeds are present inside the ripe fruit of the plant. In ancient remedies of Unani, Ayurveda, Arabic, and Chinese, the seeds and oil had been frequently used. The most common traditional applications belong to the diseases, including rheumatism, bronchitis, asthma, indigestion, diarrhea, amenorrhea, loss of appetite, and skin eruptions. It was also used as a local anesthetic and antiseptic [1].



Figure No. 1: Nigella sativa/black cumin seed and its oil

BIOACTIVE CONSTITUENTS (PHYTOCHEMICALS) IN NIGELLA SATIVA SEEDS:

Several bioactive constituents from the seed of *N. sativa* have been reported in the literature; among which Thymoquinone is considered to be the most important bioactive compound. The other main phytoconstituents reported from different varieties of *N. sativa* include sterols and saponins, alkaloids, lipid constituents, and fatty acids, phenolic compounds, and volatile oils of varying composition [4, 5]. The essential oil composition contains about forty varied compounds, amongst the abundant constituents identified, are trans-anethole, p-cymene, thymoquinone (TQ), thymohydroquinone (THQ), dithymoquinone, carvacrol, limonene, carvone, α -thujene, and β -Pinene with various concentration [6-8].

The quantity of Thymoquinone present in the volatile oil isolated by different methods of extraction from the seeds of *N. sativa* varied over a wide range: by Soxhlet extraction (2940.43 mg/kg) [9] and using SC-CO₂ (1.06, 4.07 mg/g) [10].

Various studies report the seed oil fatty acid composition (32-40%) to contain mainly, linoleic, oleic, linolenic, palmitoleic, and palmitic acids along with stearic, eicosadienoic, arachidonic, and myristic acid [8,10,11]. Novel lipids, two monoesters, and a dienoate have been isolated from the unsaponified seed extract, namely pentyl pentadec-11-enoate, methylnonadeca-15,17-dienoate, pentyl hexadec-12-enoate [12]. One of the main parts of human diet are phytosterols which are gaining interest due to their medical and nutraceutical benefits in lowering low-density lipoprotein and cholesterol levels [13]. These are useful for the assessment of the quality of vegetable oils and food labeling. The sterols identified in the black seed oil were beta sitosterol, stigmasterol, campesterol, and 5-avenasterol [11, 14]. The tocopherol content in the black seed oil varied in the range from 9.15 to 27.92 mg/100g based on diverse reports [11].

Steroidal glycosides isolated from *N. sativa* seeds which include 3-O-[β -D-xylopyranosyl-(1 \rightarrow 2)- α -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methylolean-12-enoate, stigma-5,22-dien-3- β -D-glucopyranoside [15], and 3-O-[β -D-xylopyranosyl-(1 \rightarrow 3)- α -L-rhamnopyranosyl-(1 \rightarrow 4)- β -D-glucopyranosyl]-11-methoxy-16-hydroxy-17-acetoxy hederagenin [16]. Furthermore, diverse types of alkaloids isolated from the seeds include novel Dolabellane-type diterpene alkaloids: nigellamines A1, A2, B1, and B2 and nigellamines A3, A4, A5, and C [17, 18], having lipid metabolizing activity, and indazole class of alkaloids: nigellicine, nigellidine [19, 20], and nigellidine-4-O-sulfite [21].

SCIENTIFIC RESEARCHES AND PHARMACOLOGICAL POTENTIALS

Researchers used modern scientific techniques for extensive research on *N. sativa* as it is believed to be a miraculous herb that has been used to treat multiple ailments and disorders. Numerous pharmacological properties of *N. sativa* have been investigated in the past few decades.

I. Antiviral Activity:

In a study, the NS enhances the helper-T-cell (T4) and suppressor- T-cell (T8) ratio and increases the natural killer (NK) cell activity in humans. Furthermore, it significantly inhibited the human immunodeficiency virus (HIV) protease and murine cytomegalovirus. In

the latter case, it was found to increase in number and function of the M-phi and CD4+ve T cells [1], and increased production of interferon- (INF-) gamma [22]. Interestingly, patients (30) with hepatitis C virus (HCV) infection, who were not eligible for IFN/ribavirin therapy showed significant improvement in HCV viral load (16.67% became seronegative and 50% showing significant decrease) and proved laboratory parameters such as red blood cell, total protein, platelet count, reduced fasting blood glucose, and postprandial glucose in both diabetic and nondiabetic HCV patients and decreased lower-limb edema after they are managed with black cumin seed oil [23]. According to a case report conducted by Onifade et al., after treatment with 10mL of *N. sativa* seeds twice daily for 6 months, a complete regaining and seroreversion of a 46-year-old HIV-positive patient was evidenced [24].

In another case, a 27-year-old HIV-infected woman was diagnosed during ante-natal care; she wasn't eligible for antiretroviral therapy; hence herbal therapist initiated her on honey and black cumin mixture (10mL) thrice daily for an year. The repeat serology assessments for HIV infection reported negative with undetectable viral load. The woman had 3 children (2007, 2010, and 2012) who were breastfed and none of the children were infected with HIV and her repeat CD4 count was not less than 750 cells / μ L [25].

A study conducted on 51 HIV-positive patients, administered with α -Zam which is a herbal concoction containing *N. sativa* and honey for 16 months. Within 4 weeks of commencement of α -Zam therapy, all the patients were relieved of all the signs and symptoms of HIV infection. At the end of the therapy, undetectable viral load was noted in 41 patients and less than 1000 copies/ml of viral load in the remaining 10 patients. With a decrease in viral load, the CD4 count of all participants has been increased [27]. Many *in vitro* and *in vivo* studies proved the antiviral efficacy of *N. sativa* against viruses like Murine cytomegalovirus (MCMV) [28], Avian influenza (H9N2) [29], Papaya Ring Spot Virus [30], Newcastle disease virus (NDV) [31], Hepatitis C Virus (HCV) [32], and Peste des Petits Ruminants (PPR) Virus [33]. It has been proposed that antiviral efficacy might be due to increased serum levels of interferon-gamma, higher CD4 count, augmented suppressor function and enhanced numbers of macrophages [26, 28].

Table No. 1: Studies conducted using *N. sativa*

S. No	Pharmacological action	Type of Study	No. of participants	Results	References
1.	Antiviral (Anti-HCV)	Pilot study	60	Significant decrease in viral load. Augmentation of α -fetoprotein and other liver function parameters.	[34]
2.	Antiviral (Anti-HCV)	Pilot study	195	Negative HCV-RNA	[21]
3.	Antiviral (Anti-HIV)	Pilot study	51	Undetectable viral load noted in 41 patients and less than 1000 copies/ml of viral load in 10 patients. CD4 count of all participants has been increased.	[35]
4.	Antiviral (Anti-HIV)	Pilot study	6	Undetectable viral load (HIV-RNA) in all patients. Increased body weight Increased CD4 count	[36]
5.	Antiviral (Anti-HIV)	Case report	1	Complete seroreversion. Normal CD4 count.	[24]
6.	Antiviral (Anti-HIV)	Case report	1	Sustained seroreversion. CD4 count not less than 750 cells/ μ L	[24]
7.	Antiviral (Anti-HIV)	Pilot study	30	Significant decrease in viral load. Increased Total Antioxidant Capacity (TCA). Improved laboratory biomarkers such as total protein, red blood cell, and platelet count. Decreased fasting blood glucose and postprandial glucose in both diabetic and non-diabetic HCV patients. Reduced lower-limb edema	[23]

II. Antibacterial Activity:

The modified paper disc diffusion method was used to study the antibacterial activity of ground black seeds. The growth of *Staphylococcus aureus* was observed to be inhibited by the concentration of 300 mg/mL with distilled water as control, this inhibition was confirmed by the use of positive control Azithromycin. The *N. sativa* ground seeds from Hadramout showed higher inhibition than with *N. sativa* ground seeds from Ethiopia. Thymoquinone and melanin are the two important ingredients that contribute to this positive inhibition [37].

Thymoquinone revealed broader spectrum activities against multiple strains of gram-positive and gram-negative bacteria, including Bacillus, Enterococcus, Salmonella, Serovar, Staphylococcus, Listeria, Enterococcus, Micrococcus, Pseudomonas, Escherichia, and Vibrio parahaemolyticus additionally to inhibit bacterial biofilm formation [38]. The methyl alcoholic extract of the seed showed a larger inhibition zone on gram-positive (*S. pyogenes*) as compared to gram-negative bacteria (*P. aeruginosa*, *K. pneumoniae*, and *P. vulgaris*) [39]. For various isolates of methicillin-resistant *S.aureus*, different concentrations of (100%, 80%, 50%, 40%, 30%, and 20%) *N. sativa* oils exhibited an expressively higher zone of inhibitions against all the tested bacterial strains [40]. Furthermore, black seed (2g/day) owed clinically valuable anti-H. pylori effect comparable to triple therapy [41].

III. Antifungal Activity:

The black seed oil from different regions has been reported to possess moderate inhibitory action against the pathogenic strains of yeasts, dermatophytes, and non-dermatophytic filamentous fungi along with aflatoxin-producing fungi. The *N. sativa* treatment targeted the plasma membrane, cell wall, and membranous organelles, mainly in the nuclei and mitochondria as were noticeable in the morphology of these toxigenic fungi [42]. Also, various extracts of the black seeds and TQ exhibited strong fungicidal activity against dermatophyte strains including *Trichophyton mentagrophytes* and *Microsporum gypseum* higher to fluconazole, but lower than that of ketoconazole [43]. Thymoquinone also inhibited the growth of *Aspergillus niger* and *Fusarium solani* as compared to Amphotericin-B [44], and was effective against *C. albicans*, *C. krusei*, and *C. tropicalis* [45]. The TQ also acted against *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton* spp. Also TQ, thymohydroquinone, and thymol have proved to possess antifungal activity against dermatophytes, molds, and yeasts. Moreover, the black cumin seed oil (10-200 µg/mL) was found to act against *Saccharomyces cerevisiae* and *C.utilis* [86].

IV. Antiparasitic Activity:

The seeds have schistosomicidal properties against *Schistosoma mansoni* (*in vitro*), against all stages of the parasite through a strong biocidal effect and an inhibitory action on egg-laying of adult female worms [46,47]. An ointment of black cumin seed inhibited the inflammatory reactions caused by cutaneous leishmaniasis produced experimentally in mice by subcutaneous inoculation of *Leishmania major* at the abaxial base of its tail [48]. The extract of *N. sativa* seeds at a dose of 1.25g/kg decreased *Plasmodium yoelii* infection in mice by 94%; while the effect of chloroquine was only 86% as compared to the untreated group. Also, methanolic extract of *N. sativa* reported higher parasite clearance and restoration of altered biochemical indicators by *P. yoelii* infection than chloroquine [49].

V. Antioxidant activity:

The pathogenesis of SARS-CoV-2 infection is associated with surplus production of reactive oxygen species (ROS) and a poor antioxidant system [50]. The infection can cause the overproduction of several reactive oxygen species (ROS) like H_2O_2 , $(\cdot O_2^-)$, $(\cdot OH)$, etc. through the stimulation of immunocytes like neutrophils and macrophages. Excessive ROS would oxidize cellular proteins and membrane lipids and destroy normal cells in the lung and other organs including the heart, resulting in multiple organ failure. Thus, potential antioxidants such as Vitamin E and Vitamin C (ascorbic acid) might be recommended to prevent organ damages [51]. As *N. sativa* possesses potent antioxidant properties it may help to alleviate oxidative damages to the organs. In a randomized controlled clinical trial of 50 female obese volunteer, it was found that *N. sativa* oil significantly increased the levels of superoxide dismutase (SOD) which is a major antioxidant enzyme acting against oxidative stress in the body [52]. Additionally, a placebo controlled participant blinded clinical trial of 114 type 2 diabetic patients with an equal number of volunteers in control group and *N. sativa* group, determined that the patients who received 2gm of *N. sativa* daily for 1 year have shown enhanced antioxidant defense system through significant elevation in total antioxidant capacity (TAC), glutathione levels, and superoxide dismutase (SOD) [53]. Significant decrease in plasma levels of malondialdehyde (MDA) and increased activity of erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase were reported in thirty postmenopausal women who took *N. sativa* seed along with *Allium sativum* for 2 months [54]. The bioactive constituents of *N. sativa* like thymoquinone, 4-terpineol carvacrol, and t-anethole demonstrated variable antioxidant activity [55].

Likewise, the fixed and essential oil of *N. sativa* seeds reported a significant increase in the levels of Glutathione- S-transferase (GST), glutathione reductase, and GSH-Px against oxidative stress due to potassium bromate in rats model [56]. The separate administration of nanosized clinoptilolite and black cumin seeds to Wistar rats showed a significant increase in the antioxidant parameters as compared with the concomitant uses of both extracts and diabetic groups [57]. The black seed oil and thymoquinone administration improved cisplatin-induced modification on enzymatic and nonenzymatic antioxidant defense systems, and carbohydrate biotransformation in the gastric mucosa [58].

VI. Anti-inflammatory activity:

Inflammation plays a crucial role in tissue damage caused by many chronic diseases such as cancer, diabetes, cardiovascular disorders, asthma, rheumatoid arthritis, Alzheimer's disease, epilepsy, and other infections [59]. A placebo-controlled study of 40 women with rheumatoid arthritis (RA) received *N. sativa* oil capsules (500 mg) two times daily, results showed improvement in number of inflamed joints, incidence of morning stiffness, and disease activity score [60], and a randomized, double-blind, placebo-controlled clinical trial of 42 patients suffering from rheumatoid arthritis (RA) where the participants of intervention group received 2 capsules of black cumin oil 500mg, each day for 8 weeks and the levels of malondialdehyde (MDA), and nitric oxide (NO) reduced significantly in those participants. The anti-inflammatory action of *N. sativa* is probably due to the inhibition of nuclear factor kappa B (NF- κ B) [61]. The anti-inflammatory potential of *N. sativa* was further revealed in another randomized double-blind, placebo-controlled clinical trial of 43 patients having type 2 diabetes mellitus. Among them 23 patients were assigned to an intervention group, supplemented with 500mg of *N. sativa* capsules twice daily and 20 patients were kept in the placebo group, for 8 weeks. The serum levels of nitric oxide (NO) and malondialdehyde (MDA) reduced significantly in patients supplemented with *N. sativa* [62]. Thymoquinone of black seeds inhibits the formation of leukotrienes (LTC₄ and LTB₄) in human blood cells, probably due to the inhibition of 5-lipoxygenase and LTC₄ synthase enzymes [63].

VII. Immunomodulatory effect:

Release of a large amount of pro-inflammatory cytokines is described as a cytokine storm, which results in multiple organ failure [64]. Certain constituents of black cumin seeds possess beneficial immunomodulatory effects through the augmentation of immune responses related to natural killer cells and T lymphocytes [65]. A clinical study recruited 7 healthy volunteers

and 24 patients with allergic rhinitis sensitive to house dust mites, administered with conventional doses of allergen-specific immunotherapy for 30 days. After 30 days, 12 patients among those who received 2 g/day oral suspension of black cumin resulted in a significant increase of CD8 counts and polymorphonuclear leukocyte (PMN) along with improved clinical symptoms [66]. In another study, a randomized, double-blinded placebo-controlled clinical trial of 43 female patients suffering from mild to moderate rheumatoid arthritis (RA) were administered capsules of 500mg black seed oil twice daily for 2 months, that resulted in modulation of T lymphocytes like increased percentage of CD4+CD25+ and decreased CD8+ (suppressive lymphocyte), and the ratio of CD4+/CD8+ [67].

N. sativa extract restores the resistance against granulocyte-dependent *C. albicans*. A study conducted using black seed oil suggests reduction in antibody production in typhoid vaccination, which may be due to its immunosuppressive cytotoxic effect. It was also proved that the oil corrects the imbalance caused by oxytetracycline (OXT) in leukocyte, heterophil: lymphocyte ratio, lymphocyte counts, lysosomal enzyme activity and reticuloendothelial system function. Nevertheless, it gives an immunoprotective effect when chronic administration of antibiotics occurs in pigeons. This oil also acts as a radioprotective agent against oxidative and immunosuppressive effects of ionizing radiation. In addition, an elevated level of IFN- γ with a significant decrease in pathological changes of the guinea pigs' lung was reported by black cumin oil treatment. [41,68,69]. It was also found to be protective against γ -radiation-induced damage in jejunal mucosa [70]. Furthermore, *Nigella* oil lowers thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase antibodies in Hashimoto's thyroiditis patients [71].

VIII. Antihistaminic activity:

A randomized single-blind clinical trial study of 20 patients suffering from seasonal allergic rhinitis was administered with 250 mg of black seeds orally for 15 days, resulted in a reduction of seasonal allergic rhinitis symptoms score [72]. In another randomized single-blind uncontrolled comparative clinical trial included 47 patients with seasonal allergic rhinitis who were orally administered with either montelukast (10 mg/day) or *N. sativa* (250 mg/day) for 2 weeks, randomly. On administration of *N. sativa* there was a significant reduction of daytime and ophthalmic symptoms and total eosinophil count compared to montelukast [73]. In another study, 68 allergic rhinitis patients with different severities (mild, moderate, and severe) were topically administered with a drop of black seed oil in each

nostril thrice daily for 6 weeks and the results showed that the patients with mild, moderate, and severe allergic rhinitis symptoms were relieved of 100%, 68.7% and 58.3% respectively [74]. It has been proposed that *N. sativa* may exert its antihistaminic effect through the hindrance of release of leukotrienes, histamine, and blocking histamine receptors [75].

IX. Anticoagulant activity:

In a clinical study, 94 patients (51 women and 43 men) with type 2 diabetes mellitus were randomly divided into three groups they were administered capsules containing 500 mg of grounded black cumin seeds in varied doses of 1, 2, and 3 g daily for 12 weeks. Those patients who were administered with 2 g/day of *N. sativa* seeds showed a notable increase in Partial thromboplastin time (PTT) along with the reduction in the diastolic blood pressure, systolic blood pressure, mean arterial pressure, and heart rate at the end of the study. Administration of black cumin seeds increased the PTT but not the Prothrombin Time (PT) which indicates the hindrance of the intrinsic pathway of the clotting mechanism [76]. *In vitro* coagulation assays of activated partial thromboplastin time (aPTT) and thromboelastography (TEG) by using pancreatic cancer cell lines tested the anticoagulant activity of Thymoquinone of *N. sativa* and the results showed that Thymoquinone reversed the cancer-associated thrombosis (CAT) by returning tissue factor (TF) and inflammation to basal levels. Also, Thymoquinone hindered the activity of factor Xa relatively, at higher concentrations (0.8-1.6 mg/mL) [77]. The prolongation of TT, PT and aPTT specifies that *N. sativa* inhibits the coagulation effect of extrinsic, common, and intrinsic pathways probably due to the presence of coumarin like substance [78].

X. Bronchodilatory effect:

A randomized double blind clinical trial of 15 asthmatic patients who received 50 and 100 mg/kg of boiled extract of black seeds, expressed a relatively potent bronchodilatory effect through a short significant rise in peak expiratory flow (PEF), maximal expiratory flow (MEF), maximal mid expiratory flow (MMEF), forced expiratory volume in one second (FEV1), and specific airway conductance [79]. In another randomized single-blind placebo-controlled clinical study trial, 73 asthmatic patients were divided randomly into 3 groups receiving placebo, 1 capsule of 500 mg ground seeds twice daily and 2 capsules of 500 mg ground seeds twice daily respectively, for 12 weeks along with maintained inhaled corticosteroid therapy. The patients treated with *N. sativa* showed improvements in forced expiratory volume in one second (FEV1), serum interferon- γ , peak expiratory flow (PEF),

and asthma control test (ACT) score with a reduction in fractional exhaled nitric oxide (FeNO) and serum total immunoglobulin E (IgE). Adjuvant therapy with *N. sativa* could reduce the exacerbations and improve overall control of asthma [80].

XI. Antitussive property:

The antitussive potential of *N. sativa* was studied in guinea pigs with the use of aerosols in two different concentrations of macerated and aqueous extracts, one concentration of boiled extract, and was compared to the aerosols of saline and codeine. After 10 minutes of being exposed to aerosols of different solutions, the animals were induced with coughs by the aerosol of citric acid, and it was observed that the number of coughs was less in animals exposed to *N. sativa* and codeine than compared to saline-treated animals [81]. In another study, the antitussive activity of thymoquinone from black seeds was also evaluated in guinea pigs induced with coughs by the aerosol of 20% citric acid and was compared to codeine. The number of coughs was reduced with intraperitoneal injections of thymoquinone and codeine. The antitussive activity of thymoquinone and codeine was abolished by the pretreatment of animals with naloxone (2 mg/kg) indicating that thymoquinone exerts antitussive activity by its anti-inflammatory, bronchodilatory effects mediated probably through opioid receptors [82].

CONCLUSION:

Various studies such as randomized controlled trials, case reports, pilot studies, and *in vitro* and *in vivo* studies confirmed that *N. sativa* and its main active constituent Thymoquinone possess antiviral, immunomodulatory, antioxidant, anti-inflammatory, antihistaminic, bronchodilatory, antitussive properties. The active constituents of black cumin seeds namely, nigellidine and α -hederin have been identified as potential inhibitor of antiviral diseases. Furthermore, black seeds have also shown anti-hyperlipidemic, anti-hypertensive, anti-diabetic, anti-obesity, anti-ulcer, and antineoplastic activities. Adjuvant therapy of black cumin may reduce the adverse effects of conventional medicines by helping to reduce the doses. Even so, further randomized controlled trials are required to validate the potential beneficial effects of *N. sativa* to treat the patients with different diseases, as an alternative herbal medicine.

AUTHORS CONTRIBUTIONS:

All the author have contributed equally.

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