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Sabira Sultana
University College of Conventional Medicine, Faculty of Pharmacy & Alternative Medicine, The Islamia University of Bahawalpur.

Hafiz Muhammad Asif
Department of Eastern Medicine and Surgery, Faculty of Health & Medical Sciences, the University of Poonch, Rawalakot, Aj& K, Pakistan.

Naheed Akhtar
Department of Pharmacy, Faculty of Health & Medical Sciences, the University of Poonch, Rawalakot, Aj & K, Pakistan.

Asif Iqbal
Department of Eastern Medicine, Hamdard University Karachi, Pakistan.

Haleema Nazar
Department of Eastern Medicine, Hamdard University Karachi, Pakistan.

Riaz Ur Rehman
Department of Eastern Medicine Govt. College University Faisalabad, Pakistan.

Correspondence
Sabira Sultana
University College of Conventional Medicine, Faculty of Pharmacy & Alternative Medicine, the Islamia University of Bahawalpur.

Nigella sativa: Monograph

Sabira Sultana, Hafiz Muhammad Asif, Naheed Akhtar, Asif Iqbal, Haleema Nazar, Riaz Ur Rehman

Abstract
Nigella sativa (*N. sativa*) (Family Ranunculaceae) have been used for thousands of years as a curative remedy for various disorders. *N. sativa* seed reveal a broad spectrum of pharmacological activities including immunopotentiation and antihistaminic, antidiabetic, anti-hypertensive, anti-inflammatory, and antimicrobial activities. It is known as a source of thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, 4-terpineol, t-anethol, sesquiterpene longifolene, nigellicimine and nigellicimine-N-oxide, α-pinene and thymol etc. The incalculable medicinal properties and therapeutic uses of *N. sativa* prove its importance as a valuable medicinal plant. The aim of this review is to summarize some important pharmacological studies and phytochemical investigations on *N. sativa* and isolated principles which can be investigated further to get novel molecules in the search of novel herbal drugs.

Keywords: *Nigella sativa*, medicinal plant, phytoconstituent, pharmacological activity.

Introduction
Nigella sativa (*N. sativa*) (Family Ranunculaceae) commonly known as black seed, have been used for thousands of years as a spice and food preservative, as well as a protective and curative remedy for several disorders. Traditionally, there is a common Islamic belief that blackseed is a universal remedy for all ailments, but cannot prevent aging or death. Blackseed is also known as the curative black cumin in the Holy Bible and is described as Melanthion by Hippocrates and Dioscorides and as Gith by Pliny. During the last two decades, many studies have been conducted, on the effect of *N. sativa* seed extracts on various body systems in vitro or in vivo. Seed extracts reveal a broad spectrum of pharmacological activities including immunopotentiation and antihistaminic, antidiabetic, anti-hypertensive, anti-inflammatory, and antimicrobial activities. Many of these activities have been due to the quinone constituents of the seed [1].

Taxonomic classification

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Phylum	Magnoliophyta
Class	Magnoliopsida
Order	Ranunculales
Family	Ranunculaceae
Genus	*Nigella*
Species	*N. sativa*

Common names
Black cumin, Fennel Flower, Nutmeg Flower, Black seed, Black Caraway, Roman Coriander, Damascena, Devil in-the-bush, Wild Onion Seed.

Habitat
N. sativa is native to Southern Europe, North Africa and Southwest Asia and it is cultivated in many countries in the world like Middle Eastern Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, Saudi Arabia [2].

Morphology of the plant
N. sativa is an annual flowering plant grows at 20-90 cm tall, with finely divided leaves; the flowers are white, yellow, pink, pale blue or pale purple color, with 5-10 petals.

The fruit is a large and inflated capsule consists of 3-7 united follicles, each containing several seeds [3]. Seeds are small dicotyledonous, trigonus, angular, tubercular, black externally and white inside, odor slightly aromatic and taste bitter. [4].

Fig 1: *N. sativa* flower

Fig 2: *N. sativa* seeds

Chemical composition of black seeds

The most important active constituents are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), sesquiterpene longifolene (1%-8%) α-pinene and thymol etc. Seeds contain two different types of alkaloids; i.e. isoquinoline alkaloids e.g. nigellicimine and nigellicimine-N-oxide, and pyrazol alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine. Moreover, *N. sativa* seeds also contain alpha-hederin, a water soluble pentacyclic triterpene and saponin, a potential anticancer agent [5]. Most of the pharmacological properties of *N. sativa* are mainly due to quinine constituents, of which thymoquinone is the most abundant. The seeds of *N. sativa* contain protein (26.7%), fat (28.5%), carbohydrates (24.9%), crude fibre (8.4%) and total ash (4.8 %), vitamins and minerals like Cu, P, Zn and Fe etc [6]; fatty oil rich in unsaturated fatty acids, mainly linoleic acid (50-60%), oleic acid (20%), eicodadienoic acid (3%) and dihomolinoleic acid (10%); Saturated fatty acids (palmitic, stearic acid) amount to about 30% or less. α-sitosterol is a major sterol, which accounts for 44% and 54% of the total sterols in Tunisian stigmasterol (6.57-20.92% of total sterols) [7]. Various other reported chemical components includes nigellone,avenasterol-5-ene, avenasterol- 7-ene, campesterol, cholesterol, citrostadienol, lophenol, obtusifoliol, stigmastanol, stigmasterol-7-ene, β-amyrin, butyro- spermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, 3-O-[β-D-xylopyranosyl(1→3)-α-L- rhamnopyranosyl(1→2)-α-L-arabino-pyranosyl]-28-O-[α- L-rhamnopyranosyl(1→4)-β-D-glucopyranosyl(1→6)-β-D- gluco-pyranosyl] hederagenin, volatile oil (0.5-1.6%), fatty oil (35.6-41.6%), oleic acid, esters of unsaturated fatty acids with C15 and higher terpenoids, esters of dehydrostearic and linoleic acid, aliphatic alcohol, melanthin, melanthigenin, bitter principle, tannin, resin, protein, reducing sugar, glycosidal saponin, 3-O-[β-D-xylopyranosyl-(1→2)-α-L-rhamno- pyranosyl-(1→2)-β-D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methy-lolean-12-enoate,stigma-5, 22-dien- 3-β-D-gluco-pyranoside, cycloart-23-methyl-7, 20, 22- triene-3β, 25-diol, nigellidine-4-O-sulfite, N. mines A3, A4, A5, C, N. mines A1, A2, B1, and B2 [8,9].

Medicinal uses

The seeds of *N. sativa* are used in the treatment of various diseases like bronchitis, diarrhea, rheumatism, asthma and skin disorders. It acts as a liver tonic, anti- diarrheal, appetite stimulant, emmenagogue. It is used in digestive disorders, to increase milk production in nursing mothers to fight parasitic infections, and to strengthen immune system [10]. Seeds are also used in food like flavoring additive in the breads and pickles because it has very low level of toxicity [11]. Seeds are useful in the treatment of worms and skin eruptions. Oil is used as an antiseptic and local anesthetic externally. Roasted black seeds are given internally to stop the vomiting [12].

Pharmacological activities

N. sativa has been extensively studied for its biological activities and shown to possess wide spectrum of activities such as diuretic, antihypertensive, bronchodilator, gastroprotective, hepatoprotective, antidiabetic, anticancer and immunomodulatory, analgesic, antimicrobial, analgesics and anti-inflammatory, spasmolytic, renal protective and antioxidant properties.

Antibacterial activity

Different crude extracts of *N. sativa* exhibited antimicrobial efficacy against different bacterial strains which comprised either gram negative or gram positive bacteria. Crude extracts of *N. sativa* showed a potential effect against some of the test organisms. The most effective extracts of *N. sativa* were the crude alkaloid and water extracts. Gram negative isolates were more susceptible than the gram positive ones [13].

Hannan *et al.* investigated in 2008 the antibacterial activity of *N. sativa* against clinical isolates of methicillin resistant *Staphylococcus aureus*. All tested strains of methicillin resistant *Staphylococcus aureus* in his study were sensitive to ethanolic extract of *N. sativa* at a concentration of 4 mg/disc with an MIC range of 0.2-0.5 mg/mL [13].

In another study antibacterial activity of *N. sativa* against and triple therapy in suppression of *Helicobacter Pylori* in patients with non-ulcer dyspepsia was determined. *N. sativa* seeds exhibited clinically useful anti *H. pylori* activity, comparable to triple therapy [14].

Antifungal activity

The aqueous extract of *N. sativa* seeds exhibits inhibitory effect against candidiasis in mice [15]. Antidermatophyte activity of ether extract of *N. sativa* and thymoquinone was tested against eight species of dermatophytes: four species of *Trichophyton rubrum* and one each of *Trichophyton interdigitale*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis* using Agar diffusion method. The ether extract of *N. sativa* and thymoquinone show inhibitory activity against fungal strains. The results show the potentiality of *N. sativa* as a source for antidermatophyte drugs [16].

In another study anti yeast activity of the black cumin seed quinines, dithymoquinone, thymohydroquinone, and thymoquinone were evaluated *in vitro* against six dairy spoilage yeast species. Thymohydroquinone and thymoquinone possessed significant anti yeast activity [17].

Antioxidant and antiarthritic activity

The antioxidant and antiarthritic activity of thymoquinone in Wistar rat by collagen induced arthritis was evaluated. Oral administration of thymoquinone significantly reduced the levels of pro-inflammatory mediators [IL-1β, IL-6, TNF-α, IFN-γ and PGE (2)] and increased level of IL-10 [18].

Cardiovascular activity

The acute effects of diesel exhaust particles on cardiopulmonary parameters in mice and the protective effect of thymoquinone were studied. Diesel exhaust particles were given to mice, intratracheally. Diesel exhaust particles caused systemic inflammation characterized by leucocytosis, increased IL-6 concentrations and reduced systolic blood pressure. Diesel exhaust particles reduced platelet numbers and aggravated in vivo thrombosis in pial arterioles. In vitro, addition of diesel exhausts particles to untreated blood-induced platelet aggregation. Pretreatment of mice with Thymoquinone prevented diesel exhaust particles induced decrease of systolic blood pressure and leucocytosis, increased IL-6 concentration. Thymoquinone also averted the decrease in platelet numbers and the prothrombotic events but not platelet aggregation in vitro [19].

Gastro-protective activity

Ischaemia/reperfusion (I/R) induced gastric lesion, model was used to assess the antioxidant effects of *N. sativa* oil and thymoquinone on gastric mucosal redox state and gastric lesions, 1 and 24 h after reperfusion. I/R raised the levels of lipid peroxide and lactate dehydrogenase, while diminished glutathione and superoxide dismutase. These biochemical changes were accompanied by an increase in the formation of gastric lesions, which was reduced by both treatments. *N. sativa* oil normalizes the level of lactate dehydrogenase, reduced glutathione and superoxide dismutase. These results indicate that both *N. sativa* oil and thymoquinone possess gastroprotective effect against gastric lesions which may be related to the conservation of the gastric mucosal redox state [20].

Hepatoprotective activity

Aqueous extract of the seeds of *N. sativa* were evaluated for hepatoprotective activity in male Wistar rats against carbon tetrachloride induced hepatotoxicity. Various biochemical parameters were studied to determine the hepatoprotective potential. Aqueous extract showed significant hepatoprotective effect against carbon tetrachloride-induced toxicity on the liver indicating the hepatoprotective activity [21].

Contraceptive and anti-fertility activity

Hexane extract of *N. sativa* seeds when orally administered prevented pregnancy in experimental rats at a dose of 2 g/kg daily on day's 1-10 postcoitum. [22]. In another study The 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 *N. sativa* [23].

Antioxytocic activity

N. sativa seeds oil inhibit the uterine smooth muscle contraction induced by oxytocin stimulation in rat and guinea pig uterine smooth muscles suggest the anti-oxytocic potential of *N. sativa* seeds oil [24].

Antidiabetic activity

The study was conducted to determine the effects of *N. sativa* seed ethanol extract on insulin secretion in INS832/13 and β TC-tet lines of pancreatic β-cells and on glucose disposal by C_2C_{12} skeletal muscle cells and 3T3-L1 adipocytes. Treatment with *N. sativa* amplified glucose-stimulated insulin secretion by more than 35% without affecting sensitivity to glucose. *N. sativa* treatment also accelerated β-cell proliferation. *N. sativa* increased basal glucose uptake by 55% in muscle cells and approximately 400% in adipocytes. Finally, *N. sativa* administration of pre-adipocytes undergoing differentiation accelerated triglyceride accumulation comparably with treatment with 10 μ M rosiglitazone. It is concluded that *in vivo*. Antihyperglycemic effects of *N. sativa* seed extract are attributable to a combination of therapeutically relevant insulinotropic and insulin-like properties [25].

Anticancer activity

In vitro and *in vivo* anti-cancer effects of *Nigella sativa* L. seed extracts was evaluated in one of the study. In the study the essential oil and ethyl acetate extracts were showed more cytotoxic effects against the P815 cell line than the butanol extract. Extracts showed a comparable cytotoxic effect against the ICO_1 cellline, with IC_{50} values ranging from 0.2 to 0.26% (v/v), but tests on the BSR cell line revealed a high cytotoxic effect of the ethyl acetate extract (IC_{50} = 0.2%) compared to the essential oil (IC_{50} = 1.2%) [26].

Conclusion

Medicinal plants are used for therapeutic purpose since the beginning of human civilization. They consists phytoconstituents that exhibits therapeutic potential. According to one of the report about 80% of the world population of the developing and under developed countries relies mainly on medicinal plants. It is quite obvious that the *N. sativa* is widely used in traditional medicinal system and has been reported to possess number of pharmacological activities such as hepatoprotective, anti-inflammatory, antitussive, antifungal and also used to check wounds healing and antibacterial properties. The present review summarizes

some important pharmacological studies on *N. sativa* and phytochemical investigations and isolated principles which can be investigated further to get novel molecules in the search of novel herbal drugs.

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