

# An updated review on the phytochemistry and pharmacological activity of black cumin (*Nigella sativa* L.)

Raghvendra Pandey<sup>1</sup> | Brijesh Pandey<sup>2</sup> | Atul Bhargava<sup>1</sup> 

<sup>1</sup>Department of Botany, Mahatma Gandhi Central University, Motihari, Bihar, India

<sup>2</sup>Department of Biotechnology, Mahatma Gandhi Central University, Motihari, Bihar, India

## Correspondence

Atul Bhargava, Department of Botany, Mahatma Gandhi Central University, Motihari, Bihar 845401, India.

Email: [atulbhargava@mgcub.ac.in](mailto:atulbhargava@mgcub.ac.in)

## Abstract

In this review, a comprehensive and systematic evaluation of the phytochemical constituents, traditional medicinal applications, current pharmacological research, toxicity, and nanobiotechnology of black cumin has been undertaken. An exhaustive database retrieval was conducted to collect scientific information about *Nigella sativa* L. from 1956 to 2025 using PubMed, Scopus, ISI Web of Science, SciFinder, and CABI. Search was carried out using the keywords “*Nigella sativa*,” “*Nigella* oil,” “Ethnobotany,” “Phytochemistry,” “Pharmacological activity,” “Toxicity,” and “Nanotechnology.” Several important phytochemicals are found in the seeds of *N. sativa* L., and many of which seem to have a good impact on human health and are put to important use in the Ayurvedic, Unani, and Siddha systems of medicine. Among the active compounds, thymoquinone is the most important, forming about 30%–48% of the oil fraction. Besides thymoquinone, a wide range of phytochemicals such as thymohydroquinone, dithymoquinone, *p*-cymene, sabinene, carvacrol, 4-terpineol, kaempferol (glucoside) *t*-anethol, longifolene (sesquiterpene),  $\alpha$ -pinene,  $\alpha$ -hederin (pentacyclic triterpene), and thymol have also been reported. Current research has provided scientific evidence for the traditional uses of black cumin, especially antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, anticancer, antidiabetic, neuroprotective, gastroprotective, and antiarthritic effects. The review provides an in-depth analysis of the phytochemistry, traditional uses as well as potential pharmacological properties of *N. sativa* L. Since the plant is being extensively investigated for its medicinal properties, this review provides valuable up-to-date information on the current research status and will act as a reference for future research and applications of this important medicinal plant.

## KEYWORDS

anticancer, antimicrobial, black cumin, herbal medicine, pharmacology, thymoquinone

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). *Advanced Chinese Medicine* published by John Wiley & Sons Australia, Ltd on behalf of Higher Education Press.

## INTRODUCTION

*Nigella sativa* L. (family: Ranunculaceae) is a herbaceous flowering plant used for centuries in various part of the world. Originating in southwest Asia, where it is commercially cultivated, black cummin has a rich history of use as a dietary supplement, food additive, and traditional medicine. The species is widely cultivated in the Mediterranean region, middle Europe, and vast southern and western Asia tracts [1]. India leads the world production of black cummin, with estimates of the species being grown on about 9000 ha in India, with the production of around 7000–8000 tons. The plant is also cultivated in other South Asian countries, Egypt, and Iraq, which produce black cummin in appreciable amounts [2]. Black cummin has recently gained increasing attention and has shown immense economic potential, particularly in the food and pharmaceutical sectors [3]. Considering the immense therapeutic, commercial, and industrial importance of *N. sativa*, this review comprehensively evaluates black cummin, including its phytochemical composition, traditional uses, pharmacological effects, toxicity, and potential nanobiotechnology applications.

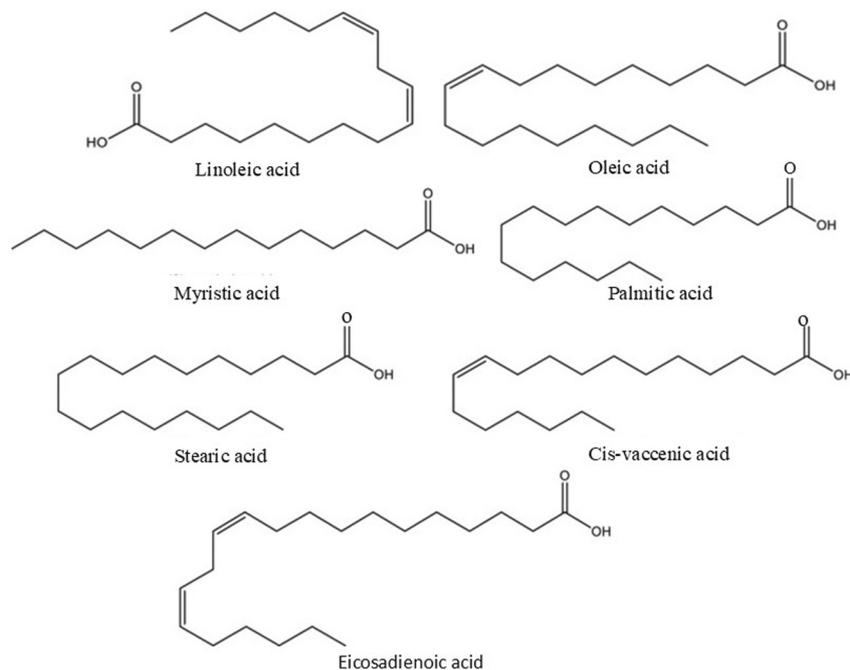
## CHEMICAL COMPOSITION

Many important nutrients are found in black cummin, facilitating its use in the Ayurvedic, Unani, and Siddha systems of medicine. Apart from being a good source of

protein (16%–19%), oil (17%–40%), carbohydrates (28.5%–33.7%), and fiber (5.5%–8.9%), the seeds are also rich in thiamine, niacin, pyridoxine, tocopherol, and a wide range of minerals [4–6]. Seeds, roots, and shoots are also known to contain appreciable amounts of carotene and vanillic acid [7]. Black cummin seed oil is rich in fatty acids, notably linoleic, linolenic, oleic, and palmitic acids along with substantial amounts of arachidonic, eicosadienoic, stearic, and myristic acids [8] (Figure 1).

Among the active compounds, thymoquinone (TQ), a monoterpene with a molecular weight of 164.20 g/mol, is the most important and forms about 30%–48% of the oil fraction [9]. Later, advanced isolation techniques established the presence of a wide range of phytochemicals such as thymohydroquinone (THQ), dithymoquinone, *p*-cymene, sabinene, carvacrol, 4-terpineol, kaempferol (glucoside), *t*-anethol, longifolene (sesquiterpene),  $\alpha$ -pinene,  $\alpha$ -hederin (pentacyclic triterpene), and thymol [10]. *Nigella* seeds also contain both isoquinoline (nigellimine and nigellimine-N-oxide) and indazole rings containing alkaloids (nigellidine and nigellicine) (Figure 2). Thus, the unique fatty acid composition and presence of a range of pharmaceutically important phytochemicals such as alkaloids, quinones, and unsaturated fatty acids, with traces of alkaloids and terpenoids make *Nigella* oil an attractive constituent for nutritional applications [11].

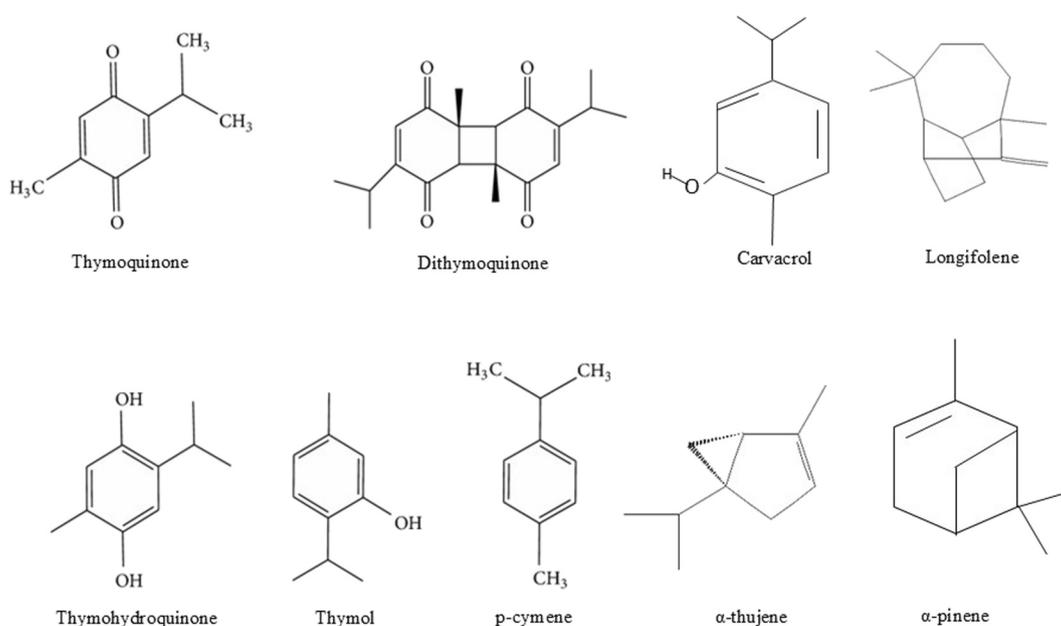
This plant is popular for its therapeutic properties due to the presence of more than a hundred chemical compounds, of which TQ is the most prominent one. Although *N. sativa* L. seeds are one of the important natural



**FIGURE 1** Fatty acids in fixed oils from *N. sativa* seeds.

sources of TQ, the phytochemical has been found in numerous plants of Lamiaceae in addition to the Ranunculaceae family (Table 1). In several plant families, TQ is available in dimeric forms such as

dithymoquinone and THQ. These are known to exhibit significant acetylcholinesterase inhibitory [20], antimicrobial [21], anticancer [22], anti-inflammatory [23], and neuroprotective [24] activity.



**FIGURE 2** Phytoconstituents reported in *N. sativa*.

**TABLE 1** Presence of thymoquinone in different plant species.

Genus-species	Family	Plant part	References
<i>Coridothymus capitatus</i> (L.) Rchb.f. Solms	Lamiaceae	Flowering branches	[12]
<i>Crotalaria saharae</i> Coss.	Leguminose	Roots	[13]
<i>Cucurbita pepo</i> L.	Cucurbitaceae	Flowers	[13]
<i>Eupatorium cannabinum</i> L.	Asteraceae	Aerial	[14]
<i>Juniperus communis</i> L.	Cupressaceae	Needle oil	[15]
<i>Monardia didyma</i> L. (chemotype 2)	Lamiaceae	Inflorescence, aerial	[14]
<i>M. media</i> Willd	Lamiaceae	Aerial	[14]
<i>M. menthifolia</i> Graham	Lamiaceae	Aerial	[14]
<i>Mosla dianthera</i> (Buch-Ham. ex Roxb.) Maxim.	Lamiaceae	Leaf	[13]
<i>Nepeta leucophylla</i> Benth.	Lamiaceae	-	[16]
<i>Nigella sativa</i> L.	Ranunculaceae	Seed	[7]
<i>Origanum syriacum</i> L.	Lamiaceae	Aerial	[17]
<i>Piper longum</i> L.	Piperaceae	Seeds	[13]
<i>Satureja montana</i> L.	Lamiaceae	Aerial	[14]
<i>Thymbra spicata</i> L.	Lamiaceae	Branch	[18]
<i>Thymus maroccanus</i> Ball.	Lamiaceae	-	[13]
<i>T. pulegioides</i> L.	Lamiaceae	Aerial	[14]
<i>T. serpyllum</i> L.	Lamiaceae	Aerial	[19]
<i>T. vulgaris</i> L.	Lamiaceae	Aerial	[14]

## FOOD AND CULINARY USES

Across diverse cultures, black cumin seeds are a popular spice and condiment. In South Asia, they are incorporated into breads, pickles, and beverages and sprinkled on salads or mixed with honey [25, 26]. In many Middle Eastern countries, the seeds are dry-roasted and used to enhance the flavor of curries and spice mixtures [26, 27].

## BLACK CUMIN IN COMPLEMENTARY AND ALTERNATIVE MEDICINAL SYSTEMS

According to ethnopharmacological investigations, several species of *Nigella* have been utilized in alternative medicinal systems and folk medical practices worldwide, highlighting their historical importance in healthcare (Table 2). The plant has been used in complementary medicine systems since the first century A.D. when Pliny referred to the plant as “Gith” [34]. Pliny further elaborated on the role of black cumin as a digestive agent and component of antidotes against snake bites [33]. In India, black cumin holds a prominent position in various traditional systems of medicine, such as Unani, Ayurveda, and Siddha [9]. The plant is

considered a remedy for all diseases except death and is suggested for regular consumption in “Tibb-e-Nabwi.” Black cumin's historical importance as a medicinal plant is evident in its mention as a curative black seed in the Bible and as “Melanthion” by ancient scholars such as Hippocrates and Dioscorides [34, 35].

Asia has witnessed widespread use of *N. sativa* in traditional medicinal systems as well as in folk medicine. Black cumin has been mentioned in Ayurveda, the traditional Indian system of medicine, for its medicinal and health benefits [36]. The Pharmacopoeia of India recommends 0.5–4 g of *N. sativa* L. seed powder as a stimulant to relieve bowel, as a carminative, and in digestive disorders [7]. In India and Bangladesh, it is also used to treat menstrual discomfort and diabetes [7, 37]. In Pakistan, the plant is used by medical practitioners known as “Hakims” as a sexual tonic, in diabetes, for lactation, and against bacterial infections [38], whereas in Iran, the plant is used as an anthelmintic, antiparasitic, antitussive, digestive, and as a remedy for dysmenorrhea [39]. In Mauritius, Nepal, Thailand, Bangladesh, and several Middle Eastern Asian countries, the species is widely used and regarded as a panacea for its therapeutic properties [33, 40].

Black cumin has also been utilized in several African countries for a long time. The plant has been used in traditional Algerian medicine as a remedy against

**TABLE 2** Medicinal uses of *Nigella sativa* as reported in the traditional systems of medicine.

Vernacular name	Medicinal uses	Country	References
Ayurveda system			
Kalonji/Mangrail/Kalaunji	Known to balance <ul style="list-style-type: none"> <li>• Vata (movement energy)</li> <li>• Kapha (structure and lubrication energy)</li> </ul>	India	[26, 28, 29]
Unani system			
Habatut Barakah Shooneez/Habba Sauda/Habb al-barka/Kamun eswid/Habbat al-barakah	<ul style="list-style-type: none"> <li>• Stomachic</li> <li>• Laxative</li> <li>• Carminative</li> <li>• Galactagogue</li> <li>• Inflammation</li> <li>• Ascites</li> <li>• Jaundice</li> <li>• Piles</li> <li>• Tertian fever</li> <li>• Paralysis</li> <li>• Eye diseases</li> </ul>	Saudi Arabia, Pakistan, Iran, Egypt, and Turkey	[26–28]
Chinese medicine			
Hei Zhong Cao	<ul style="list-style-type: none"> <li>• Digestive system</li> <li>• Soothing stomach pains</li> <li>• Spasms</li> <li>• Bloating</li> </ul>	China	[30, 31]
Miscellaneous			
Black seed/Fennel flower/Nutmeg flower/Roman coriander	<ul style="list-style-type: none"> <li>• Headaches</li> <li>• Cough and asthma</li> <li>• Kidney stones</li> </ul>	England	[32, 33]

bacterial infections, diabetes, and high blood pressure. Furthermore, Bedouins, the nomadic Arab tribe inhabiting parts of Egypt, use the plant stem as a remedy for jaundice and the seeds for high blood pressure and heart diseases [33]. In Morocco, the seeds and leaves of black cumin are taken orally in the form of powder, herbal tea, decoction, or inhalant to cure diabetes, allergy, otolaryngological, urological, and nephrological disorders [33, 41].

## PHARMACOLOGICAL ACTIVITIES OF *N. SATIVA*

The numerous medicinal benefits of the plant are ascribed to TQ, an essential oil ingredient classified as "Generally Recognized as Safe" (GRAS) by the FDA. The key pharmacological properties of the plant and its phytoconstituents include anticonvulsant, antimicrobial, anticancer, antipyretic, antihistaminic, antidiabetic, anti-inflammatory, and antioxidant.

### Antioxidant

Various progressive pathological disorders such as neurological dysfunction (Parkinson's and Alzheimer's disease), chronic obstructive pulmonary disease, rheumatoid arthritis (RA), and endocrine illness are correlated to oxidative stress and an increase in free radical levels [42]. Black cumin has been identified for its potent antioxidant activity in both in vivo and in vitro investigations [43].

A substantial drop was observed in malondialdehyde (MDA) levels in the plasma of normal postmenopausal women after ingesting *Allium sativum* and *N. sativa* seeds for two months. Along with this, enhanced activity was observed in erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in the studied sample [44]. Similarly, in the case of oxidative stress induced by potassium bromate in a rodent model, black cumin seed oil showed a considerable increase in GST, glutathione reductase, and GSH-Px [45].

Separate treatment of black cumin and nano-sized clinoptilolite has revealed a substantial increment in antioxidant enzymes that were higher than the concurrent administration in Wistar rats [46]. The methanolic extract and cumin seed oil successfully refilled over 80% of the plasma total antioxidant potential by 88% and efficiently mitigated lipidemic oxidative stress in atherogenic suspension [47]. Likewise, *N. sativa* oil (NSO) and TQ treatment markedly ameliorated cisplatin-stimulated changes in both antioxidant and carbohydrate biotransformation enzymes in adult male Wistar rats [48]. It was concluded that NSO and TQ served as potential novel antioxidant agents that can be employed as important nutrients to promote health and avoid diseases [43]. The

evaluation of *N. sativa* essential oil's antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS), ferric ion reduction, and SOD enzymatic assays offers important information about its capacity to neutralize reactive oxygen species (ROS) and safeguard oral tissues [49]. These results are important because antioxidants assist the maintenance of oral health and the prevention of illness by preventing oxidative damage to cells and tissues. In another study, the capacity of cold-pressed black cumin oil, TQ, and THQ was assessed for the superoxide scavenging activity [50]. Their findings demonstrated that, although THQ has two para-hydroxyl groups, it had no impact on the scavenging of the superoxide radical, whereas oil and TQ are potent scavengers [50].

### Antidiabetic

Diabetes mellitus is a metabolic condition defined by persistently elevated levels of glucose in the blood, mainly due to the weakened ability of the body to produce or respond to insulin [51]. Neuropathy, nephropathy, retinopathy, coronary heart disease, accelerated atherosclerosis, and gastrointestinal and genitourinary dysfunctions are some of the problems associated with diabetes [52]. Conventional medicine is a comparatively low-cost healthcare option for diabetes patients but is marred by several side effects [53]. Several studies have proved that plant and seed extract of black cumin improved disease outcomes in alloxan or streptozotocin (STZ)-induced diabetes in rodents through enhanced antioxidant activity, regulation of blood lipids, and improved tissue regeneration (Table 3) [63–66]. Furthermore, the biological production of silver nanoparticles (AgNPs) using the seed extract has shown promise in treating diabetic neuropathy by targeting inflammation, oxidative stress, and nerve growth factor production [67]. Another in vitro cell-free experiment has shown that silver nanoparticles produced from NSO have  $\alpha$ -amylase inhibitory activity, confirming its hypoglycemic effects [62].

NSO displayed antidiabetic benefits in rodent models that have been attributed to its multifaceted actions, including promoting cell survival and suppressing apoptosis, stimulating growth factor signaling and reducing inflammation, enhancing insulin and antioxidant production, inhibiting extracellular matrix gene expression, and favorably altering lipid profiles [68–70]. As shown in Table 3, findings from various preclinical and clinical trials suggest that black cumin and NSO can serve as useful herbal medications for treating diabetes and associated disorders. According to Shaukat et al. [71], ROS levels increase as diabetes worsens and have previously been linked to beta cell death. TQ is valuable as a possible treatment despite

**TABLE 3** Anti-diabetic effects of black cumin.

Form of ns	Plant part used	Model/System	Duration	Result observed	References
Extract	Seed	Alloxan induced diabetic rabbit	2 months	↓ Increased conc. of glucose and lipid peroxidation and ↓ glutathione and ceruloplasmin and ameliorated biochemical and histological sign of liver damage	[54]
Oil	Seed oil	Streptozotocin- diabetic rats	2, 4, and 6 weeks	↓ Blood glucose	[55]
Aqueous extract	Seed	Streptozotocin- diabetic rats	30 days	↓ Levels of glucose serum	[56, 57]
TQ	Seed component	Streptozotocin-diabetic rats	-	Inhibit the COX-2 enzyme expression, lipid peroxidation and MDA levels, ↑SOD level in pancreatic tissue	[58]
Aqueous extract		Streptozotocin- diabetic rats		↓Oxidative stress and preserved pancreatic beta cell integrity	[59]
TQ	Seed component	Streptozotocin-induced diabetic hamsters	30 days	↓ Fasting blood glucose and glycated HB levels, ↓glyconeogenesis	[60]
TQ	Seed component	Streptozotocin-NA-induced diabetic rats	-	↑ Insulin and glycemic status ↓ plasma glucose	[61]
Silver nanoparticles	NSO	In vitro biochemical assay	-	Decrease $\alpha$ amylase activity	[62]

Abbreviations: COX-2, cyclooxygenase-2; HB, hemoglobin; MDA, malondialdehyde; NSO, *Nigella sativa* oil; SOD, superoxidase dismutase; TQ, thymoquinone.

its lack of action on nuclear factor kappa-B (NF- $\kappa$ B), a transcription factor whose activation by oxidative stress is a precursor to diabetes [71].

## Antibacterial

One of the significant health challenges in the 21st century is a steep increase in bacterial infections and the development of resistance among microbes. Medicinal plants have been at the forefront of biological research as potential sources of novel antimicrobial agents, driven by the pressing need to combat rising antimicrobial resistance [72, 73]. Many such research studies have been initiated to assess the antibacterial properties of black cumin seeds. Studies have confirmed that black seed extract possesses strong antibacterial properties, including activity against several strains of bacteria that have developed resistance to multiple drugs. This finding underscores the potential of black seed extract in addressing the growing challenge of antibiotic resistance. According to Babu et al. [74], TQ exhibited strong antibacterial activity against *Staphylococcus aureus*, with minimum inhibitory concentration (MIC) values for most isolates ranging from 2 to 8  $\mu$ g/mL. Furthermore, the essential oil found in NSS (*N. sativa* seed) exhibits moderate effectiveness against some bacteria, such as *S. aureus* and *Bacillus subtilis*, and efficiently suppresses intestinal parasites [75]. Spherical-shaped platinum nanoparticles with sizes between 1 and 6 nm synthesized using black cumin seed extract have shown strong antimicrobial activity [76] against Gram-positive and

negative types at 100 and 500  $\mu$ g/mL concentrations, respectively [77]. Likewise, polyethylene glycol-capped graphene oxide nanoparticles loaded with *N. sativa* seed extract were evaluated for efficient drug delivery against *S. aureus* and *E. coli* by Jihad et al. [78]. The results exhibited increased cell wall permeability, reduced cell wall integrity, and nucleic acid damage in the bacterial cells.

## Antiviral

Quite a few recent research studies have assessed the antiviral activity of black cumin extract. Barakat et al. [79] reported significant results with respect to the effect of NSO against hepatitis C virus (HCV). HCV-infected subjects who could not receive interferon (IFN)- $\alpha$  were administered NSO in capsules. A drop in total viral count was observed after three months of three-times-daily treatment. A rise in antioxidant activity indicated a decrease in RBCs and platelet hemolysis. The blood glucose levels and lower limb edema were also significantly reduced. These results showed the efficacy of black cumin in reducing viral load in HCV patients and improved oxidative stress and carbohydrate management in diabetic subjects. Black cumin and its derivatives have been found to be highly effective in controlling a range of viral infections in animals, namely coronavirus [80], Newcastle disease virus [81], and peste des petits ruminants virus [82]. When compared to the control group, *N. sativa* dramatically decreased the risk of death in COVID-19 patients. This effect only applied to early treatment; late therapy commencement

did not lower mortality risk [80]. The plant and its major component, TQ, have proved to be efficient in managing plant viruses such as *the broad bean mosaic virus* [83], *tobacco mosaic virus* [84], and *zucchini yellow mosaic virus* [85, 86].

## Antifungal

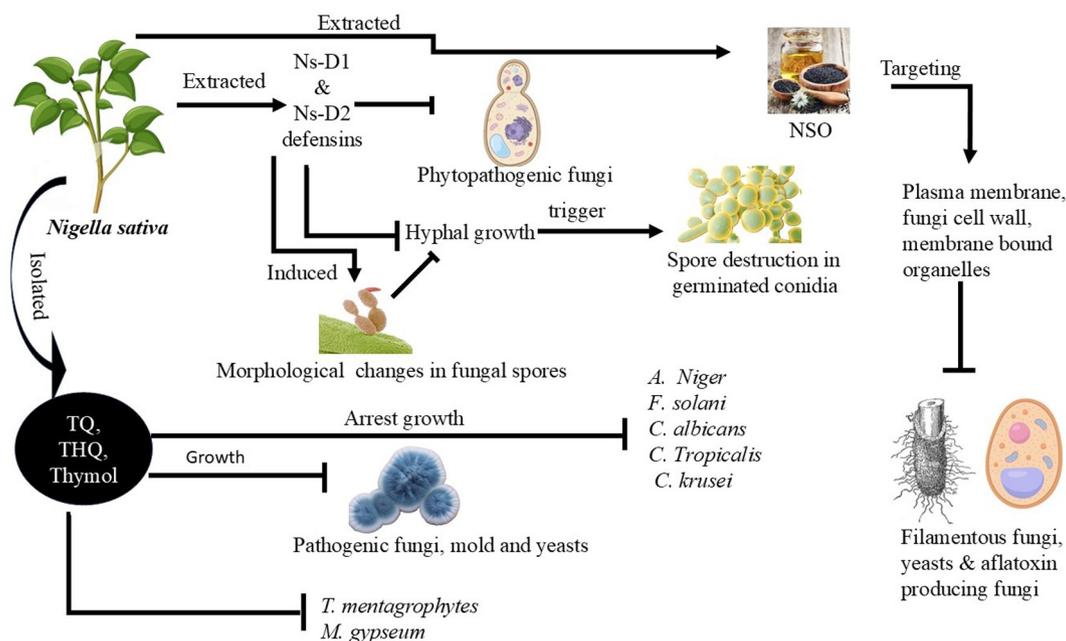
TQ, THQ, and thymol exhibit potent antifungal action against several pathogenic fungi, molds, and yeasts [87–89]. Rogozhin et al. [88] isolated two novel defensins from black cumin, namely Ns-D1 and Ns-D2, which displayed significant antifungal activity against a range of phytopathogenic fungi.

Black cumin defensins (Ns-D1 and Ns-D2) showed potent antifungal activity with IC<sub>50</sub> values below 10 µg/mL for most tested fungi. Although spore germination was unaffected, the defensins inhibited hyphal growth and triggered spore destruction in germinated conidia. Interestingly, Ns-D2 exhibited more vigorous antifungal activity than Ns-D1 against several species, including *Bipolaris sorokiniana*, *Fusarium oxysporum*, *B. cinerea*, and the potato blight pathogen *Phytophthora infestans*. Both defensins showed similar efficacy against *Fusarium* species, with an MIC of 55 mg/mL, resulting in 81%–86% growth inhibition. In addition to inhibiting hyphal growth, the defensins induced morphological changes in fungal spores, with varying effects across different genera. Therefore, the powerful antifungal activity of black cumin defensins makes them ideal candidates for developing fungus-resistant plants (Figure 3).

Black cumin seed oil is known to exhibit significant inhibitory action against filamentous fungi, yeasts, and even aflatoxin-producing fungi. NSO primarily acts by targeting the plasma membrane, fungal cell wall, and membrane-bound organelles [90]. TQ and extracts of black cumin have also displayed strong fungicidal action against *Trichophyton mentagrophytes* and *Microsporum gypseum*, which are superior to that reported for fluconazole [91]. TQ also arrests the development of *A. niger* and *F. solani*, the activity being similar to *amphotericin-B*, a macrocyclic, polyene, antifungal agent [92], and has been quite effective against *Candida albicans*, *C. tropicalis*, and *C. krusei* [93]. Thus, black cumin's significant antifungal action warrants further exploration and use in the food and pharmaceutical industries.

## Neuroprotection

The importance of black cumin as a promising neuropharmacological medicine in facilitating learning and memory has recently been exhaustively examined [94–96]. The hydroalcoholic extracts of *N. sativa* seeds were assessed with respect to memory and oxidative damage to brain tissues during pentylenetetrazole-induced seizures [97]. According to Mahmoud Janloo et al. [98], the reduced MDA levels in the brain support the idea that giving *N. sativa* for two weeks might enhance memory and reduce lipid peroxidation. Antioxidant enzymes such as SOD therefore rose dramatically. *N. sativa* may alleviate oxidative damage and cognitive impairment in mice receiving cisplatin. As a



**FIGURE 3** Antifungal mechanism of *N. sativa*. Ns-D1, *Nigella sativa* D1; Ns-D2, *Nigella sativa* D2; NSO, *Nigella sativa* oil; THQ, thymohydroquinone; TQ, thymoquinone.

result, *N. sativa* may be a useful dietary supplement to help chemotherapy patients avoid neurotoxicity [98]. It was observed that *N. sativa* enhanced antioxidant effects in the rat brain and prevented learning and memory impairments. In another study, treatment with 1 mL/kg of black cumin oil for 14 days prevented elevation of hippocampal nitric oxide (NO) levels, enhanced synthesis of neurogenic proteins such as Ki67<sup>+</sup>, improved acetylcholinesterase (AChE) action, and reduced depletions of neuro-cognitive indicators after chlorpyrifos treatment in rats [99]. NSO is also known to significantly enhance neurocognitive indices such as Morris water maze (MWM).

## Anticancer

Black cumin contains anti-proliferative, cytotoxic, and anti-metastatic properties as evidenced by many research studies [100] (Table 4). Several phytochemicals such as dithymoquinone, THQ, carvacrol, thymol, nigellimine-N-oxide, nigellidine, and nigellidine have been implicated in the anticancer activities exhibited by the plant. Treatment of black cumin seed extract, seed oil, TQ, and nanoemulsion to different cancer cell lines has shown significant alteration in cell morphology, reduction in cell viability and cell proliferation, along

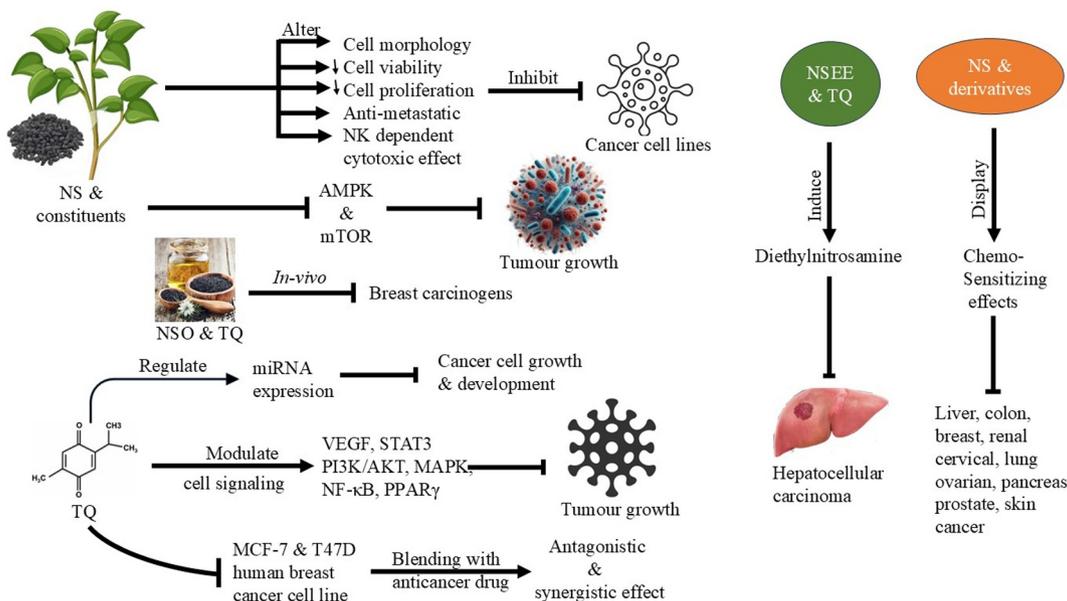
with anti-metastatic and NK-dependent cytotoxic effects [101, 103]. *N. sativa* and its derivatives display significant chemo-sensitizing effects and have been found to be highly effective in liver, colon, breast, renal, cervical, lung, ovarian, pancreatic, prostate, and skin cancers. Most of the effects were attributed to the presence of TQ in the cumin derivatives. Another in vivo investigation indicated that NSO and TQ had a protective effect against breast carcinogens at doses ranging from 1 to 10 mg/kg [108]. Shahin et al. [100] proposed that regular supplementation of black cumin ethanolic seed extract (150–350 mg/kg), TQ (20 mg/kg), and silymarin reduced the hepatocellular carcinoma proliferation induced by diethylnitrosamine, an extremely potent carcinogen (Figure 4).

TQ has shown potent antitumor activity through its ability to modulate different cell signaling pathways such as VEGF, bcl2/bax ratio, STAT3, PI3K/AKT, MAPK, NF- $\kappa$ B, and PPAR $\gamma$  [109]. The evidence supporting the therapeutic benefits of phytochemicals derived from NS in the treatment of breast cancer is strengthened by the network pharmacology and molecular docking study and its experimental validation as reported by Arif et al. [110]. As a result, these phytochemicals can be considered as promising candidates for the development of novel anticancer agents against breast cancer [110]. The blend of anticancer drugs and

**TABLE 4** Anticancer activities of *Nigella sativa* plant parts.

Types of cancer	Form of ns	Experimental model	Result observed	References
Breast cancer	Seed extract, NSO, nanoemulsion	Human breast cancer cell line (MCF-7)	↓ Cell viability, ↑ apoptosis, alter cellular morphology with IC50 value 0.41–82 $\mu$ L/mL	[101]
	TQ	Human breast cancer cell line	Potent therapeutic adjuvant with IC50 = 64.93 and T47D, IC50 = 165 $\mu$ mol/L, antagonistic and synergistic effect	[102]
Liver cancer	Ethanolic seed extract, TQ and silymarin	Diethylnitrosamine induced hepatocellular carcinoma in albino-Wistar rat model	↓ p-EGRF, p-ERK1/2, deactivation of EGRF/ERK1/2 signaling, ↓ c-fos, PCNA, Bcl2, ↓ cell proliferation, ↓ alpha-fetoprotein (AFP), hepatic enzyme, ↑ antioxidant	[100]
Cervical cancer	TQ	HeLa cervical cell line	Dose-dependent antiproliferative effect	[103]
Colon cancer	NSO	Wister rats-colon cancer induced with carcinogens	↓ Reduced malignant and benign colon tumor sizes, incidences and multiplicities	[104]
Gastric cancer	TQ	Gastric cancer cell line	↑ Apoptosis	[105]
Renal cancer	TQ	Renal cell cancer cell lines (786-O and ACHN)	↓ Migration, invasion and epithelial–mesenchymal transition, ↓ metastasis by induction of autophagy via AMPK/mTOR signaling	[106]
Pancreatic cancer	TQ	Pancreatic ductal adenocarcinoma cell lines (AsPC1 and MiaPaCa-2)	↓ Bcl-2 and HDAC, ↑ apoptosis and G2 cell cycle arrest, ↓ cell viability, ↓ reduce tumor size, ↑ p53 and p21	[107]

Abbreviations: Bcl2, B-cell lymphoma 2; c-fos, proto-oncogene; EGRF, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase; G2, growth 2; HDAC, histone deacetylases; IC50, inhibitory concentration; p21, cyclin-dependent kinase inhibitor; p53, tumor suppressor protein; PCNA, proliferating cell nuclear antigen; p-EGRF, phosphorylated epidermal growth factor receptor; p-ERK1/2, phospho-extracellular signal-regulated kinase; T47D, ductal carcinoma.



**FIGURE 4** Anticancer mechanism of *N. sativa*. AKT, applied knowledge test; AMPK, adenosine monophosphate activated protein kinase; MAPK, mitogen-activated protein kinase; MCF-7, michigan cancer foundation-7; mTOR, mammalian target of rapamycin; NF- $\kappa$ B, nuclear factor kappa B; NK, natural killer; NS, *Nigella sativa*; NSEE, *Nigella sativa* ethanolic extract; PI3K, phosphoinositide 3-kinases; PPAR $\gamma$ , peroxisome proliferator-activated receptors; STAT3, signal transducer and activator of transcription-3; VEGF, vascular endothelial growth factor.

TQ synergistically affects cancer cell viability and mortality. TQ has been found to be a potent therapeutic adjuvant against human breast cancer cell lines MCF-7 [111] and T47D and was reported to have both antagonistic and synergistic effects when used with anticancer drugs [102]. The most recent approach involving TQ in cancer therapy utilizes targeting miRNAs, which are considered hallmarks for cancer diagnosis and therapy. TQ has the unique ability to interfere with various signaling pathways and regulate the expression of miRNAs, preventing cancer cell growth and development [112].

Different studies have confirmed the presence of several saponins, such as  $\alpha$ -hederin and Nigella (A–D), which may play a significant role in protecting against cancer. Interestingly, when compared to vehicle-administered mice, Nigella A and B reduced tumor growth in mice, possibly mediated through an AMPK-activated autophagy and mTOR inhibition [113].

## Antiarthritic

Arthritis is the inflammatory illness of joints and stiffness primarily affecting the elderly. RA is characterized by synovial membrane inflammation, swelling, and generation of autoantibodies in serum and synovial fluid [114, 115]. NSO and TQ have been demonstrated to be useful against arthritis, particularly RA, due to their powerful anti-inflammatory properties. Several

studies have pointed toward the antiarthritic potential of NSO and TQ [116, 117]. TQ has been seen as an effective therapeutic agent for the treatment of osteoarthritis because it is known to suppress IL-1 $\beta$ -induced prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), NO, and MMP synthesis in chondrocytes, which leads to the inhibition of inflammation [118].

A placebo-controlled experiment investigated the usefulness of black cumin seed powder for the treatment of inflammatory conditions. Significant improvement was observed in the treated individuals with no side effects [119]. The pain-relieving effect of black cumin oil in geriatric individuals afflicted with osteoarthritis was evaluated by Tuna et al. [120]. Applying NSO without massaging led to a considerable reduction of knee pain in osteoarthritis patients. A similar experiment involving topical application of NSO for 21 days witnessed a significant drop in osteoarthritis pain in people aged between 60 and 80 [121]. The mean pain score before NSO administration was  $75 \pm 16.29$ , which reduced to  $38.88 \pm 17.84$  after 21 days of treatment. Nasuti et al. [122], determined the antiarthritic potential of NSO in a rat model of arthritis using two doses viz. 1.82 and 0.91 mL/kg. NSO minimized the loss in body mass, decreased the injected hind paw volume, and reduced proinflammatory mediators. It was concluded that a higher dose of NSO (1.82 mL/kg) was quite efficient in controlling arthritis during the acute phase but was ineffective in the chronic phase. The chondroprotective effects of intraarticular injection of

0.3 ml *whole NSO* for five weeks in a rabbit osteoarthritis model were first evaluated by Turhan et al. [123]. The intraarticular injections reduced the cartilage deterioration in the early stages of osteoarthritis. The anti-arthritis effect of TQ in FCA-induced arthritic rats was assessed by Arjumand et al. [124]. Administration of TQ reduced the arthritic score through decreased paw swelling and improved inflammatory signs without any hepatotoxic or nephrotoxic effects. There was also a considerable reduction in the mRNA levels of toll-like receptor 2 (TLR2), TLR4, IL-1, NF- $\kappa$ B, and TNF- $\alpha$ . Black seed is also known to cure a number of illnesses by inhibiting the inflammatory cytokine TNF- $\alpha$ . The plant also exhibits potent anti-inflammatory, gastro-protective, neuroprotective, analgesic, antitussive, and antioxidant properties [125]. A study investigating the effect of black cumin extracts in collagen-induced arthritic mice showed reduced inflammation and neutrophil infiltration score [126]. All these studies support the anti-inflammatory and immunomodulatory properties of *N. sativa* and its components.

### Anti-inflammatory and analgesic

Inflammation, a normal part of the body's defense involving local response to cellular injury, is involved in numerous medical disorders, including autoimmune diseases, asthma, depression, type 2 diabetes (T2D), cancer, and gastrointestinal and neurodegenerative disorders. Anti-inflammatory medicines currently available in the market fall into two categories: those that cause significant side effects such as gastric ulcers, adrenal suppression, hyperglycemia, glycosuria, and psychic disorders when used for an extended period of time, and others that are free from these effects [43]. *N. sativa* L. could be beneficial in this respect since its vast array of novel compounds could be utilized to develop anti-inflammatory drugs with few adverse effects. According to Wahab and Alsayari [127], *N. sativa* has been found to be useful in a wide range of ailments, including chronic inflammatory disorders. Similar to indomethacin, NSO and TQ have shown potent anti-inflammatory effects during acute inflammation in Albino Wistar rats through inhibitory effects on the peripheral mediators [128]. Zakaria et al. [129] performed an acetic acid-induced writhing test on a rodent model. They found less abdominal constrictions and hindlimb elongation in mice treated with an aqueous extract of *N. sativa*. Compared to diclofenac sodium, the alcoholic extract of the plant exhibited a significant pain-relieving effect in mice [130]. TQ's anti-inflammatory activities might be due to its ability to block cyclooxygenase and lipoxygenase enzymes, reducing the oxidative products of arachidonic acid production, such as thromboxane B<sub>2</sub> and leukotriene [43].

### PROTECTION AGAINST EMERGING DISEASES

The pharmacological potential of black cumin and some of its components against severe acute respiratory syndrome coronavirus-2 (SARSCoV-2), the infectious agent responsible for the recently emerged COVID-19 disease associated with unprecedented spread and high mortality, have been documented in several *in silico* investigations [131–133]. The effectiveness of black cumin and its components against SARSCoV-2 in cell lines and animal models have been effectively evaluated in a recent study [134]. According to Ashraf et al. [135], honey and *N. sativa* considerably decreased mortality, accelerated viral load clearance, and improved symptoms in COVID-19 patients compared to a placebo. They also reported no negative effects connected to honey and *N. sativa* administration. TQ also exhibits antiviral properties against human immunodeficiency virus (HIV). Chandra et al. [136] assessed the efficacy of black seed oil against the long-term effects of highly active antiretroviral therapy (HAART) in HIV-1-positive Sprague–Dawley rats and obtained a decrease in HAART-related hyperinsulinemia after a seven-month administration. A middle-aged HIV patient was entirely cured and stayed seronegative for six months after being treated with a black cumin mixture [137]. Another study by the same group evaluated the mix of honey and *N. sativa* L. seeds on a 27-year-old HIV-positive woman who had not been on antiviral medication [138]. It was observed that the treatment eliminated all the HIV-infected cells from the body, leading to sustained sero-reversion and complete removal of the virus. Despite positive results, these investigations have been inconclusive due to the small sample size and lack of replicability. Thus, detailed studies are required to confirm the antiviral activity of black cumin seed against HIV using a large sample size.

### EFFECTS ON MEMORY AND COGNITION

Several studies showed the beneficial effects of black cumin constituents on memory in animal models. In experimental mice with traumatic brain injury, the treatment of *N. sativa* extract demonstrated notable neuroprotective benefits against memory impairment and synaptic dysfunction [139]. Bin Sayeed et al. [140] examined the impact of black cumin on mood, anxiety, and cognition in healthy adolescent human males aged between 14 and 17 years using *N. sativa* L. capsules for four weeks. It was observed that using black cumin as a nutritional supplement stabilized mood, decreased anxiety, and positively modulated cognition. The effects of black cumin extract administration in concentrations ranging from 100 to 400 mg/kg during neonatal and juvenile growth on learning and memory were evaluated by

Beheshti et al. [141] in female Wistar rats. Experiments using the MWM, passive avoidance (PA) test, and determination of total thiol and MDA concentrations revealed that dietary supplementation with black cumin extract during developmental stages significantly improved learning and memory along with enhancement in oxidative stress criteria in hippocampal and cortical tissues. The same group further explored the potential benefits of black cumin extract, specifically examining its impact on learning and memory impairments linked to hypothyroidism in rodents using MWM and PA tests, along with total thiol and MDA concentration. The results proved that different doses of black cumin extract attenuated hypothyroidism-induced learning and memory impairment in female Wistar rats comparable to vitamin C. This was probably due to an enhancement in the total thiol concentrations in brain tissues and a reduction in MDA concentrations. It was concluded that these protective effects were due to the prevention of oxidative damage against brain tissues.

Elilbol et al. [142] evaluated the effects of TQ in 6-month-old female Sprague–Dawley rats in which amyloid beta 1–42 ( $A\beta_{1-42}$ ) was infused into the right hippocampus. No significant decline was observed in either the learning or memory performance of  $A\beta$ -treated rodents. TQ treatment improved memory in treated rats through increased hippocampal cell number and decreased fibril deposition, plaque formation, and neuron degeneration. Additionally, TQ attenuated the expression of mir29c, miR26b, and Bax and decreased the beta-site APP cleaving enzyme 1 protein expression. Thus, TQ displayed recovery capability during Alzheimer's disease by removing amyloid beta plaques and increasing neuronal viability, leading to memory consolidation. Kadil and Filali [143] assessed the effects of *Nigella* oil on cognitive decline in rats through behavioral evaluation, carried out different tests, and pointed out the therapeutic effect of NSO on cognitive decline. Many others have attributed the neuro-regenerative effects of TQ to modulation in the mitogen-activated protein kinase (MAPK) pathway, probably through the activation of JNK protein, upregulation of mir-124, and downregulation of ERK1/2 and NOS enzymes [144]. Thus, TQ is an efficient and promising natural neuroprotective agent that can be developed into a safe therapeutic intervention for the treatment of neurological disorders.

## CLINICAL TRIALS AND TOXICITY ISSUES

Clinical investigations have verified several reported effects of black cumin and its derivatives in animal models, both in vitro and in vivo [145, 146]. Results carried out on T2D patients to assess the therapeutic effects of *N. sativa* L. have shown significant reduction in blood glucose [147], C-reactive protein, total cholesterol (TC),

low-density lipoprotein cholesterol (LDL-C), triglyceride, 2-h postprandial blood glucose (2hPG), and hemoglobin A1c or glycated hemoglobin (HbA1c), as well as an enhancement in  $\beta$ -cell function, glomerular filtration rate, insulin, and serum high-density lipoprotein cholesterol (HDL-C) levels [131, 146]. A nonrandomized clinical trial involving 57 T2D patients administered black cumin seed capsules for 1 year showed a substantial decrease in TC, LDL-C, TC/HDL-C, LDL-C/HDL-C ratios, diastolic blood pressure, mean arterial pressure, and heart rate, as well as a surge in serum HDL-C level as compared to control [148]. *N. sativa* trials have also been carried out for obesity, dyslipidemia, skin diseases, neurological disorders, infertility, infectious diseases, and respiratory disorders [146]. Clinical studies have revealed the promising potential of black cumin in preventing and treating metabolic diseases, underscoring its versatility as a therapeutic agent.

Despite the euphoria surrounding the pharmacological effects of black cumin, studies on the toxicity aspect have also been undertaken. Several studies have pointed out that seed extract and its constituents exhibit low level of toxicity. The LD50 value of TQ was found to be 2.4 g/kg (range 1.52–3.77) [149], but high doses (2 g/kg) caused respiratory disorders. A more recent study evaluated the toxic effect of black cumin powder on the liver function in Sprague–Dawley rats through histological study and the assessment of liver enzymes, namely alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [150]. No significant alteration in ALT and AST levels was observed between the control and treated groups. At the same time, histological studies exhibited negligible variations in fatty degeneration even at high doses and without inflammation and necrosis. No toxicity and liver dysfunction were observed with a dose of 1 g/kg supplemented for four weeks, thus proving the safety of black cumin powder.

## NANOTECHNOLOGY AND *N. SATIVA*

The recent spurt in nanobiotechnological research has led to biomedical applications. *N. sativa* L. has gained attention in developing functionalized nanomaterials and is being extensively researched for green synthesis of nanoparticles for biomedical applications. AgNPs have been one of the most popular metal nanoparticles among nanobiotechnologists [151]. Rohini et al. [152] undertook the green synthesis of AgNPs by mixing 1 mM  $AgNO_3$  solution with an aqueous seed extract of black cumin and tested their efficacy against human breast cancer (MCF-7). The AgNPs with a 100–150 nm size range exhibited dose-dependent cytotoxicity (1–200  $\mu$ g/mL) and altered the expression of Bax and Bcl-2 proteins and the inflammatory marker COX-2. Spherical AgNPs of ~25 nm were biologically synthesized using ethanolic extract from black cumin seeds [67]. Treatment of diabetic

neuropathy rats with AgNPs alone and combined with *N. sativa* L. extract served as potent neuroprotective agents against inflammation and oxidative stress. Silver-platinum bimetallic nanoparticles (N@Pt-Ag BNPs) have also been produced using the ethanolic extract of black seed. Characterization of the nanoparticles showed spherical morphology with a size of 5.6 nm. The N@Pt-Ag BNPs showed high efficacy against breast cancer cell lines and potent antibacterial activity against *B. subtilis*, *E. coli*, and methicillin-resistant *S. aureus* (MRSA). The high catalytic activity of the nanoparticles was quite effective in the photodegradation of azo dyes [153].

Apart from silver, there are also reports of metal and metal oxide nanoparticle synthesis using other metals [76, 78]. Green synthesis of gold nanoparticles (AuNPs) using chloroauric acid and *N. sativa* L. extract was carried out by Fragoon et al. [154]. Crystalline and poly-shaped biocompatible AuNPs were produced that were suggested to be used for in vivo imaging and therapy. Dhandapani et al. [155] undertook green synthesis of novel AuNPs, Curto-Cumin AuNP (CC-AuNP), using black cumin seed extract and membrane vesicles of *Curtobacterium proimmune*. The anticancer activity of the newly synthesized nano entities was evaluated against human gastric adenocarcinoma (AGS) cells. It was observed that CC-AuNP led to the production of ROS, upregulated apoptotic signaling, and suppressed the autophagy-related signaling pathway production, pointing toward the potential of CC-AuNPs as an effective anticancer agent.

## FUTURE PROSPECTS AND CHALLENGES

*N. sativa* offers a safe remedy for several diseases owing to the presence of a wide range of bioactive compounds such as TQ, THQ, dithymoquinone, nigellimine, nigellidine, quercetin, p-cymene,  $\alpha$ -thujene, longifolene,  $\beta$ -pinene,  $\alpha$ -pinene, and carvacrol [156]. However, a lot needs to be done to modulate its role in pharmaceutical development. TQ has low bioavailability (58%) and high hydrophobicity or lipophilicity (log  $p = 2.54$  value), which impedes its incorporation in traditional dosage forms such as tablets and capsules. In addition, its extremely thermolabile nature further limits its use in pharmaceutical formulations. This has led to rapid research through nanobiotechnology that would enable its incorporation in formulation, especially the development of nanoformulations. Encapsulation of TQ using hydrophilic biodegradable polymers such as polyethylene glycol (PEG) can significantly improve solubility and systemic bioavailability [157]. This novel approach may overcome the hindrance in pharmaceutical development and increase the TQ's bioavailability

without compromising efficacy and safety. The bioactive components of black cumin can boost the effectiveness of other medications such as chemotherapy or antibiotics through lower doses, which can lead to better results and help overcome issues such as drug resistance. Apart from this, in-depth studies are required to assess the efficacy of TQ in monotherapy and as an adjuvant, along with clear insights into the toxicological profile so that it can be safely used in higher quantities and for longer times.

## AUTHOR CONTRIBUTIONS

**Raghvendra Pandey:** Writing—original draft; writing—review and editing. **Brijesh Pandey:** Writing—review and editing. **Atul Bhargava:** Conceptualization; supervision; writing—review and editing.

## CONFLICT OF INTEREST STATEMENT

All the authors declare no financial/commercial conflicts of interest.

## ORCID

Atul Bhargava  <https://orcid.org/0000-0003-0386-1642>

## REFERENCES

1. Dzoeyem JP, McGaw LJ, Kuete V, Bakowsky U. Anti-inflammatory and anti-nociceptive activities of African medicinal spices and vegetables. Medicinal Spices and Vegetables from Africa. *Africa Acad Press Elsev UK*. 2017:239-270.
2. Huchchannanavar S, Yogesh LN, Prashant SM. The black seed *Nigella sativa*: a wonder seed. *Intern J Chem Stud*. 2019;7:1320-1324.
3. Burdock GA. Assessment of black cumin (*Nigella sativa* L.) as a food ingredient and putative therapeutic agent. *Regul Toxicol Pharmacol*. 2022;128:105088.
4. El-Naggar T, Gómez-Serranillos MP, Palomino OM, Arce C, Carretero ME. *Nigella sativa* L. seed extract modulates the neurotransmitter amino acids release in cultured neurons *in vitro*. *BioMed Res Int*. 2010;2010:398312-398318.
5. Saxena SN, Rathore SS, Diwakar Y, et al. Genetic diversity in fatty acid composition and antioxidant capacity of *Nigella sativa* L. genotypes. *LWT*. 2017;78:198-207.
6. Mukhtar H, Mumtaz MW, Tauqeer T, Raza SA. Composition of *Nigella sativa* seeds. In: Fawzy Ramadan M, ed. *Black Cumin (Nigella sativa) Seeds: Chemistry, Technology, Functionality, and Applications*. Food Bioact Ingred Sprin; 2021:45-57.
7. Salehi B, Quispe C, Imran M, et al. *Nigella* plants – traditional uses, bioactive phytoconstituents, preclinical and clinical studies. *Front Pharmacol*. 2021;12:1-26.
8. Piras A, Rosa A, Falconieri D, Porcedda S, Dessi MA, Marongiu B. Extraction of oil from wheat germ by supercritical CO<sub>2</sub>. *Molecules*. 2009;14(7):2573-2581.
9. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of *Nigella sativa*: a miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337-352.
10. Kabir Y, Akasaka-Hashimoto Y, Kubota K, Komai M. Volatile compounds of black cumin (*Nigella sativa* L.) seeds cultivated in Bangladesh and India. *Helv*. 2020;6(10):e05343.
11. Mehraj T, Elkanayati RM, Farooq I, Mir TM. A review of *Nigella sativa* and its active principles as anticancer agents. *Pharmacol Therap Appl Elsev*. 2022;2022:91-118.

12. Fleisher Z, Fleisher A. Volatiles of *Coridothymus capitatus* chemotypes growing in Israel: aromatic plants of the Holy Land and the Sinai. Part XV. *J Essent Oil Res.* 2002;14(2):105-106.
13. Pedersen JA. Distribution and taxonomic implications of some phenolics in the family Lamiaceae determined by ESR spectroscopy. *Biochem Systemat Ecol.* 2000;28(3):229-253.
14. Taborsky J, Kunt M, Kloucek P, Lachman J, Zeleny V, Kokoska L. Identification of potential sources of thymoquinone and related compounds in Asteraceae, Cupressaceae, Lamiaceae, and Ranunculaceae families. *Cent Eur J Chem.* 2012;10(6):1899-1906.
15. Mastelić J, Miloš M, Kuštrak D, Radonic A. Essential oil and glycosidically bound volatile compounds from the needles of common juniper (*Juniperus communis* L.). *Croat Chem Acta.* 2000;73:585-593.
16. Gupta GN, Talwar YP, Nigam MC, Handa KL. The essential oil of *Nepeta leucophylla*. *Soap Perfum Cosmet.* 1964;37:45-46.
17. Lukas B, Schmiderer C, Franz C, Noval J. Composition of essential oil compounds from different Syrian populations of *Origanum syriacum* L. (Lamiaceae). *J Agric Food Chem.* 2009;57(4):1362-1365.
18. Fleisher Z, Fleisher A. Extract analyses of *Satureja thymbra* L. and *Thymbra spicata* L. aromatic plants of the Holy Land and the Sinai. Part XVII. *J Essent Oil Res.* 2005;17(1):32-35.
19. Aziz S, Irshad M, Asghar SF, Hussain H, Ahmed I. Phytotoxic and antifungal activities of essential oils of *Thymus serpyllum* grown in the state of Jammu and Kashmir. *J Essen Oil-Bear Plants.* 2010;13:224-229.
20. Ansari M, Mandegary A, Mosalanejad N, Asadi A, Shariffifar F. *Nigella sativa* L, supplementary plant with anticholinesterase effect for cognition problems: a kinetic study. *Curr Aging Sci.* 2020;13(2):129-135.
21. Talebi M, Talebi M, Farkhondeh T, Samarghandian S. Biological and therapeutic activities of thymoquinone: focus on the Nrf2 signaling pathway. *Phytother Res.* 2021;35(4):1739-1753.
22. Alhmied F, Alammar A, Alsultan B, Alshehri M, Pottoo FH. Molecular mechanisms of thymoquinone as anticancer agent. *Combinat. Chem High Through Screen.* 2021;24(10):1644-1653.
23. Ali MY, Akter Z, Mei Z, Zheng M, Tania M, Khan MA. Thymoquinone in autoimmune diseases: therapeutic potential and molecular mechanisms. *Biomed Pharmacother.* 2021;134:111157.
24. Isaev NK, Chetverikov NS, Stelmashook EV, Genrikhs EE, Khaspekoy LG, Illarioshkin SN. Thymoquinone as a potential neuroprotector in acute and chronic forms of cerebral pathology. *Biochemist.* 2020;85(2):167-176.
25. Pandey R, Pandey B, Bhargava A. Morphological and anatomical studies in *Nigella sativa* L. (Ranunculaceae). *J Appl Hortic.* 2024;26(2):159-164.
26. Srinivasan K. Cumin (*Cuminum cyminum*) and black cumin (*Nigella sativa*) seeds: traditional uses, chemical constituents, and nutraceutical effects. *Food Qual Saf.* 2018;2:1-16.
27. Yarnell E, Abascal K. *Nigella sativa*: holy herb of the middle east. *Alternative Compl Ther.* 2011;17(2):99-105.
28. Sharma P, Yelne MB, Dennis TJ, Joshi A, Billore K. *Database on Medicinal Plants Used in Ayurveda*. Central Council for Research in Ayurveda and Siddha, Ministry of Health and Family Welfare, Govt. of India; 2000.
29. Ramadan MF. Nutritional value, functional properties and nutraceutical applications of black cumin (*Nigella sativa* L.): an overview. *Intern J Food Sci Tech.* 2007;42(10):1208-1218.
30. Grieve A. *Modern Herbal*. Penguin; 1984.
31. Chevallier A. *The Encyclopedia of Medicinal Plants*. Dorling Kindersley; 1996.
32. Duke JA. *Duke's Handbook of Medicinal Plants of Latin America*. RC press; 2008.
33. Hossain MS, Sharfaraz A, Dutta A, et al. A review of ethnobotany, phytochemistry, antimicrobial pharmacology and toxicology of *Nigella sativa* L. *Biomed Pharmacother.* 2021;143:112182.
34. Heiss AG, Stika HP, De Zorzi N, Jursa M. *Nigella* in the mirror of time a brief attempt to draw a genus' ethnohistorical portrait. *Offa.* 2012;69/70:147-169.
35. Khan MA. Thymoquinone, a constituent of prophetic medicine-black seed, is a miracle therapeutic molecule against multiple diseases. *Int J Health Sci.* 2019;13:1-2.
36. Kaur G, Invally M, Khan MK, Jadhav P. A nutraceutical combination of *Cinnamomum cassia* and *Nigella sativa* for type 1 diabetes mellitus. *J Ayurveda Integr Med.* 2018;9:27-37.
37. Hossain MS, Jindal H, Maisha S, et al. Antibacterial effects of 18 medicinal plants used by the Khyang tribe in Bangladesh. *Pharm Biol.* 2018;56(1):201-208.
38. Aziz MA, Khan AH, Adnan M, Iztullah I. Traditional uses of medicinal plants reported by the indigenous communities and local herbal practitioners of Bajaur Agency, Federally Administered Tribal Areas. *Pak J Ethnopharmacol.* 2017;198:268-281.
39. Bahmani M, Tajeddini P, Ezatpour B, Kopaei MR, Naghdi N, Asadi-Samani M. Ethnobotanical study of medicinal plants against parasites detected in Shiraz, southern part of Iran. *Pharm Lett.* 2016;8:153-160.
40. Alrawi SN, Khidir A, Elnashar MS, et al. Traditional Arabic and Islamic medicine: validation and empirical assessment of a conceptual model in Qatar. *BMC Compl Alternative Med.* 2017;17(1):157.
41. Toneu IT, Martin GJ, Ouhammou A, Puri RK, Hawkins JA. An ethnomedicinal survey of a Tashelhit-speaking community in the High Atlas, Morocco. *J Ethnopharmacol.* 2016;188:96-110.
42. Lupoli F, Vannocci T, Longo G, Niccolai N, Pastore A. The role of oxidative stress in Friedreich's ataxia. *FEBS Lett.* 2018;592(5):718-727.
43. Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. *Nigella sativa* L. (black cumin): a promising natural remedy for wide range of illnesses. *Evid Base Complem Alter Med.* 2019;2019:1528635.
44. Mostafa RM, Moustafa YM, Mirghani Z, Al-Kusayer GM, Moustafa KM. Antioxidant effect of garlic (*Allium sativum*) and black seeds (*Nigella sativa*) in healthy postmenopausal women. *Sage Open Med.* 2013;1:2050312113517501.
45. Sultan MT, Butt MS, Karim R, et al. *Nigella sativa* fixed and essential oil modulates glutathione redox enzymes in potassium bromate induced oxidative stress. *BMC Compl Alternative Med.* 2015;15(1):330.
46. Omid H, Khorram S, Mesgari M, Jafarabadi MA, Esfaniani AT. Effects of separate and concurrent supplementation of nano-sized clinoptilolite and *Nigella sativa* on oxidative stress, antioxidative parameters and body weight in rats with type 2 diabetes. *Biomed Pharmacother.* 2017;96:1335-1340.
47. Ahmad S, Beg ZH. Evaluation of therapeutic effect of omega-6 linoleic acid and thymoquinone enriched extracts from *Nigella sativa* oil in the mitigation of lipidemic oxidative stress in rats. *Nutrition.* 2016;32(6):649-655.
48. Shahid F, Farooqui Z, Khan AA, Khan F. Oral *Nigella sativa* oil and thymoquinone administration ameliorates the effect of long-term cisplatin treatment on the enzymes of carbohydrate metabolism, brush border membrane, and antioxidant defense in rat intestine. *Naunyn-Schmiedeberg Arch Pharmacol.* 2018;391(2):145-157.
49. Bhavikatti SK, Zainuddin SLA, Ramli RB, et al. Insights into the antioxidant, anti-inflammatory and anti-microbial potential of

- Nigella sativa* essential oil against oral pathogens. *Sci report*. 2024;14(1):11878.
50. Sakib R, Caruso F, Aktar S, et al. Antioxidant properties of thymoquinone, thymohydroquinone and black cummin (*Nigella sativa* L.) seed oil: scavenging of superoxide radical studied using cyclic voltammetry, DFT and single crystal X-ray diffraction. *Antioxidants*. 2023;12(3):607.
  51. Pandey R, Singh C. *Application of Fungi and Their Metabolite in Human Health Care*. Mycotalk. AkiNik Publications; 2023:331-361.
  52. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: an overview. *Avic J Med*. 2020;10(4):174-188.
  53. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. *Front Endocrinol*. 2017;8:6.
  54. Meral I, Yener Z, Kahraman T, Mert N. Effect of *Nigella sativa* on glucose concentration, lipid peroxidation, anti-oxidant defence system and liver damage in experimentally-induced diabetic rabbits. *J Veter Med*. 2001;48(10):593-599.
  55. El-Dakhakhny M, Mady N, Lember N, Ammon HP. The hypoglycemic effect of *Nigella sativa* oil is mediated by extra pancreatic actions. *Planta Med*. 2002;68(5):465-466.
  56. Kanter M, Meral I, Yener Z, Ozbek H, Demir H. Partial regeneration/proliferation of the  $\beta$ -cells in the Islets of Langerhans by *Nigella sativa* L. in streptozotocin-induced diabetic rats. *Tohoku J Exp Med*. 2003;201(4):213-219.
  57. Kaleem M, Kirmani D, Asif M, Ahmed Q, Bano B. Biochemical effects of *Nigella sativa* L seeds in diabetic rats. *Ind J Experim Biol*. 2006;44:745-748.
  58. Al Wafai R. *Nigella sativa* and thymoquinone suppress cyclooxygenase-2 and oxidative stress in pancreatic tissue of streptozotocin-induced diabetic rats. *Pancre*. 2013;42:841-849.
  59. Kanter M, Coskun O, Korkmaz A, Oter S. Effects of *Nigella sativa* on oxidative stress and  $\beta$ -cell damage in streptozotocin-induced diabetic rats. *Disc Mol Cellu Evol Biol*. 2004;9(1):685-691.
  60. Fararh KM, Shimizu Y, Shiina T, Nikami H, Ghanem MM, Takewaki T. Thymoquinone reduces hepatic glucose production in diabetic hamsters. *Res Vet Sci*. 2005;79(3):219-223.
  61. Pari L, Sankaranarayanan C. Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin-nicotinamide induced diabetic rats. *Life Sci*. 2009;85(23-26):830-834.
  62. Preeti R, Anitha R, Rajeshkumar S, Lakshmi T. Anti-diabetic activity of silver nanoparticles prepared from cummin oil using alpha amylase inhibitory assay. *Internat J Res Pharmaceut Sci*. 2020;11:1267-1269.
  63. Mohebbati R, Abbasnezhad A. Effects of *Nigella sativa* on endothelial dysfunction in diabetes mellitus: a review. *J Ethnopharmacol*. 2020;252:112585.
  64. Touati KB, Kacimi G, Haffaf EM, Berdia S, Bouguerra SA. *In vivo* subacute toxicity and antidiabetic effect of aqueous extract of *Nigella sativa*. *Evid Base Complem Altern Med*. 2017;2017(1):8427034.
  65. Abbasnezhad A, Niazmand S, Mahmoudabady M, et al. *Nigella sativa* L. seed regulated eNOS, VCAM-1 and LOX-1 genes expression and improved vasoreactivity in aorta of diabetic rat. *J Ethnopharmacol*. 2019;228:142-147.
  66. Nourbar E, Mirazi N, Yari S, Rafieian-Kopaei M, Nasri H. Effect of hydroethanolic extract of *Nigella sativa* L. on skin wound healing process in diabetic male rats. *Intern J Preven Med*. 2019;10(1):18.
  67. Alkhalaf MI, Hussein RH, Hamza A. Green synthesis of silver nanoparticles by *Nigella sativa* extract alleviates diabetic neuropathy through anti-inflammatory and antioxidant effects. *J Biol Sci*. 2020;27(9):2410-2419.
  68. Abdelrazek HMA, Kilany OE, Muhammad MAA, Tag HM, Abdelazim AM. Black seed thymoquinone improved insulin secretion, hepatic glycogen storage, and oxidative stress in streptozotocin-induced diabetic male wistar rats. *Oxid Med Cell Longev*. 2018;2018(1):8104165.
  69. Altun E, Avci E, Yildirim T, Yildirim S. Protective effect of *Nigella sativa* oil on myocardium in streptozotocin-induced diabetic rats. *Acta Endocrinol*. 2019;15:289-294.
  70. Akhtar MT, Qadir R, Bukhari I, et al. Antidiabetic potential of *Nigella sativa* L seed oil in alloxan-induced diabetic rabbits. *Trop J Pharmaceut Res*. 2020;19(2):283-289.
  71. Shaukat A, Zaidi A, Anwar H, Kizilbash N. Mechanism of the antidiabetic action of *Nigella sativa* and Thymoquinone: a review. *Front Nutr*. 2023;10:1126272.
  72. Srivastava S. Bacterial integrons. *Biotechnology: recent trends and emerging dimensions*. *Tayl Fran USA*. 2018:57-74.
  73. Srivastava S, Dashora K, Ameta KL, et al. Cysteine-rich antimicrobial peptides from plants: the future of antimicrobial therapy. *Phytother Res*. 2021;35(1):256-277.
  74. Babu B, Rao P, Suman E, Udayalaxmi J. A study of antibacterial effect of *Nigella sativa* seed extracts on bacterial isolates from cases of wound infection. *Infect Disord Drug target*. 2023;23(5):e030423215400.
  75. Abbas M, Gururani MA, Ali A, et al. Antimicrobial properties and therapeutic potential of bioactive compounds in *Nigella sativa*: a review. *Molecules*. 2024;29(20):4914.
  76. Pandey R, Srivastava S. Plant thionins. The green antimicrobial agents. In: *book: Integrative Approaches to Biotechnology*. CRC Press; 2024:93-110.
  77. Ayguna A, Gülbagca F, Ozer LY, et al. Biogenic platinum nanoparticles using black cummin seed and their potential usage as antimicrobial and anticancer agent. *J Pharmaceut Biomed Anal*. 2020;179:112961.
  78. Jihad MA, Noori F, Jabir MS, Albukhaty S, Al-Malki FA, Alyamani AA. Polyethylene glycol functionalized graphene oxide nanoparticles loaded with *Nigella sativa* extract: a smart antibacterial therapeutic drug delivery system. *Molecules*. 2021;26(11):3067.
  79. Barakat EMF, El Wakeel LM, Hagag RS. Effects of *Nigella sativa* on outcome of hepatitis C in Egypt. *World J Gastroenterol*. 2013;19:2529-2536.
  80. Umer M, Naveed A, Maryam Q, et al. *Nigella sativa* for the treatment of COVID-19 patients: a rapid systematic review and meta-analysis of randomized controlled trials. *Food Sci Nutr*. 2023;12(3):2061-2067.
  81. Khan AU, Tipu MY, Shafee M, et al. In-ovo antiviral effect of *Nigella sativa* extract against new castle disease virus in experimentally infected chicken embryonated eggs. *Pak Veter J*. 2018;38:434-437.
  82. Aqil K, Khan RM, Aslam A, et al. In vitro antiviral activity of *Nigella sativa* against Peste des petits ruminants (PPR) Virus. *Pakistan J Zool*. 2018;50(6):2223-2228.
  83. Mohamed EF. Inhibition of Broad bean mosaic virus (BBMV) using extracts of *Nigella* (*Nigella sativa* L.) and *Zizyphus* (*Zizyphus spina-christi* Mill.) plants. *Journal Am Sci*. 2011;7:727-734.
  84. El-Sayed MSS. *Chemical Studies on Constituents of Some Antiviral Plant Extracts* Ain PhD Thesis. Faculty of Agriculture, Shams University, Egypt; 2011.
  85. Abdel-Shafi S. Preliminary studies on antibacterial and antiviral activities of five medicinal plants. *J Plant Pathol Microbiol*. 2013;04:1-8.
  86. Elbeshehy EKF. Inhibitor activity of different medicinal plants extracts from *Thuja orientalis*, *Nigella sativa* L, *Azadirachta indica* and *Bougainvillea spectabilis* against Zucchini yellow

- mosaic virus (ZYMV) infecting *Citrullus lanatus*. *Biotechnol Biotechnol Equip.* 2017;3(2):270-279.
87. Taha M, Azeiz A, Saudi W. Antifungal effect of thymol, thymoquinone and thymohydroquinone against yeasts, dermatophytes and non-dermatophyte molds isolated from skin and nails fungal infections. *Egypt J Biochem Mol Biol.* 2010;28(2).
88. Rogozhin EA, Oshchepkova YI, Odintsova TI, et al. Novel antifungal defensins from *Nigella sativa* L. seeds. *Plant Physiol Biochem.* 2011;49(2):131-137.
89. Pandey R, Pandey B, Bhargava A. The emergence of *N. sativa* L. as a green antifungal agent. *Mini Rev Med Chem.* 2024;24(16):1521-1534.
90. Shokri H. A review on the inhibitory potential of *Nigella sativa* against pathogenic and toxigenic fungi. *Avice J Phytomed.* 2016;6:21-33.
91. Mahmoudvand H, Sepahvand A, Jahanbakhsh S, Ezatpour B, Mousavi SAA. Evaluation of antifungal activities of the essential oil and various extracts of *Nigella sativa* and its main component, thymoquinone against pathogenic dermatophyte strains. *J Mycol Med.* 2014;24(4):e155-e161.
92. Aljabre SHM, Alakloby OM, Randhawa MA. Dermatological effects of *Nigella sativa*. *J Dermatol Dermatol Surg.* 2015;19(2):92-98.
93. Piras A, Rosa A, Marongiu B, et al. Chemical composition and in vitro bioactivity of the volatile and fixed oils of *Nigella sativa* L. extracted by supercritical carbon dioxide. *Indust Crop Prod.* 2013;46:317-323.
94. Beheshti F, Khazaei M, Hosseini M. Neuropharmacological effects of *Nigella sativa*. *Avice J Phytomed.* 2016;6:104.
95. Sahak MKA, Kabir N, Abbas G, Draman S, Hashim NH, Hasan Adli DS. The role of *Nigella sativa* and its active constituents in learning and memory. *Evid Base Complem Altern Med.* 2016;2016(1):6075679.
96. Gawas CG, Mathur S, Wani M, Tabassum H. *Nigella sativa* and its nano-mediated approach toward management of neurodegenerative disorders: a review. *Ibrain.* 2023;9(1):111-123.
97. Vafaei F, Hosseini M, Hassanzadeh Z, et al. The effects of *Nigella sativa* hydro-alcoholic extract on memory and brain tissues oxidative damage after repeated seizures in rats. *Iran J Pharm Res (IJPR).* 2015;14:547.
98. Mahmoud JanlooY, Attari FS, Roshan S, et al. Effect of hydro-alcoholic extract of *Nigella sativa* on cisplatin-induced memory impairment and brain oxidative stress status in male rats. *Avice J Phytomed.* 2024;14:13-22.
99. Imam A, Lawal A, Oyewole LA, et al. *Nigella sativa* conserved hippocampal oxidative and neurogenic activities to salvage neuro-cognitive integrities in chlorpyrifos insult. *Scient Afr.* 2018;1:e00008.
100. Shahin YR, Elguindy NM, Abdel Bary A, Balbaa M. The protective mechanism of *Nigella sativa* against diethylnitrosamine-induced hepatocellular carcinoma through its antioxidant effect and EGFR/ERK1/2 signaling. *Environ Toxicol.* 2018;33(8):885-898.
101. Periasamy VS, Athinarayanan J, Alshatwi AA. Anticancer activity of an ultrasonic nanoemulsion formulation of *Nigella sativa* L. essential oil on human breast cancer cells. *Ultrason Sonochem.* 2016;31:449-455.
102. Bashmil HA, Alamoudi AA, Noorwali A, Hegazy GA, Ajabnoor G, Al-Abd AM. Thymoquinone influences the anticancer properties of paclitaxel and gemcitabine against breast cancer cells. *Can Res.* 2018;78(13\_Supplement):5813.
103. Butt AS, Nisar N, Ghani N, Altaf I, Mughal TA. Isolation of thymoquinone from *Nigella sativa* L. and *Thymus vulgaris* L. and its anti-proliferative effect on HeLa cancer cell lines. *Trop J Pharmaceut Res.* 2019;18(1):37-42.
104. Salim EI. Cancer chemo preventive potential of volatile oil from black cumin seeds, *Nigella sativa* L. in a rat multi-organ carcinogenesis bioassay. *Oncol Lett.* 2010;1(5):913-924.
105. Lei X, Lv X, Liu M, et al. Thymoquinone inhibits growth and augments 5-fluorouracil-induced apoptosis in gastric cancer cells both in vitro and in vivo. *Biochem Biophys Res Commun.* 2012;417(2):864-868.
106. Zhang Y, Fan Y, Huang S, et al. Thymoquinone inhibits the metastasis of renal cell cancer cells by inducing autophagy via AMPK/mTOR signaling pathway. *Cancer Sci.* 2018;109(12):3865-3873.
107. Relles D, Chipitsyna GI, Gong Q, Yeo CJ, Arafat HA. Thymoquinone promotes pancreatic cancer cell death and reduction of tumor size through combined inhibition of histone deacetylation and induction of histone acetylation. *Adv Preven Med.* 2016;2016:1407840-1407849.
108. Linjawi SAA, Khalil WKB, Hassanane MM, Ahmed ES. Evaluation of the protective effect of *Nigella sativa* extract and its primary active component thymoquinone against DMBA-induced breast cancer in female rats. *Arch Med Sci.* 2015;11:220-229.
109. Almatroodi SA, Almatroodi A, Alsahli MA, Khan AA, Rahmani AH. Thymoquinone, an active compound of *Nigella sativa*: role in prevention and treatment of cancer. *Curr Pharm Biotechnol.* 2020;21(11):1028-1041.
110. Arif R, Bukhari SA, Mustafa G, Ahmed S, Albeshri MF. Network pharmacology and experimental validation to explore the potential mechanism of *Nigella sativa* for the treatment of breast cancer. *Pharmaceut.* 2024;17(5):617.
111. Vahitha V, Lali G, Prasad S, Karupiah P, Karunakaran G, Al-Salhi M. Unveiling the therapeutic potential of thymol from *Nigella sativa* L. seed: selective anticancer action against human breast cancer cells (MCF-7) through down-regulation of cyclin D1 and proliferative cell nuclear antigen (PCNA) expressions. *Mol Biol Rep.* 2024;51(1):61.
112. Homayoonfal M, Asemi Z, Yousefi B. Targeting long non coding RNA by natural products: implications for cancer therapy. *Crit Rev Food Sci Nutr.* 2023;63(20):4389-4417.
113. Chen L, Han H, Amin A, Zhang L, Ma S. Hydrolysis product of *Nigella* A obtained from *Nigella glandulifera* Freyn seeds promotes apoptosis and AMPK-mediated autophagy in human colon cancer SW620 cells. *Arch Biol Sci.* 2018;70(4):603-612.
114. Van Delft M, Huizinga T. An overview of autoantibodies in rheumatoid arthritis. *J Autoimmun.* 2020;110:102392.
115. Hannan MA, Rahman MA, Sohag A, et al. Black Cumin (*Nigella sativa* L.): a comprehensive review on phytochemistry, health benefits, molecular pharmacology, and safety. *Nutrition.* 2021;13(6):1784.
116. Mahboubi M, Mohammad Taghizadeh Kashani L, Mahboubi M. *Nigella sativa* fixed oil as alternative treatment in management of pain in arthritis rheumatoid. *Phytomedicine.* 2018;46:69-77.
117. Khabbazi A, Javadi Z, Seyedsadjadi N, Malek Mahdavi A. Systematic review of the potential effects of *Nigella sativa* on rheumatoid arthritis. *Planta Med.* 2020;86(07):457-469.
118. Wang D, Qiao J, Zhao X, Chen T, Guan D. Thymoquinone inhibits IL-1 $\beta$ -induced inflammation in human osteoarthritis chondrocytes by suppressing NF- $\kappa$ B and MAPKs signaling pathway. *Inflammation.* 2015;38(6):2235-2241.
119. Salimzadeh A, Ghourchian A, Choopani R, Hajimehdipoor H, Kamalinejad M, Abolhasani M. Effect of an orally formulated processed black cumin, from Iranian traditional medicine pharmacopoeia, in relieving symptoms of knee osteoarthritis: a prospective, randomized, double-blind and placebo-controlled clinical trial. *Inter J Rheum Dis.* 2017;20(6):691-701.
120. Tuna HI, Babadag B, Ozkaraman A, Balci Alparslan G. Investigation of the effect of black cumin oil on pain in

- osteoarthritis geriatric individuals. *Compl Ther Clin Pract.* 2018;31:290-294.
121. Azizi F, Ghorat F, Hassan Rakhshani M, Rad M. Comparison of the effect of topical use of *Nigella sativa* oil and diclofenac gel on osteoarthritis pain in older people: a randomized, double-blind, clinical trial. *J Herb Med.* 2019;16:100259.
  122. Nasuti C, Fedeli D, Bordoni L, et al. Anti-inflammatory, anti-arthritis and anti-nociceptive activities of *Nigella sativa* oil in a rat model of arthritis. *Antioxidants.* 2019;8(9):342.
  123. Turhan Y, Arıcan M, Karaduman ZO, et al. Chondroprotective effect of *Nigella sativa* oil in the early stages of osteoarthritis: an experimental study in rabbits. *J Musculoskelet Neuronal Interact.* 2019;19:362.
  124. Arjumand S, Shahzad M, Shabbir A, Yousaf MZ. Thymoquinone attenuates rheumatoid arthritis by downregulating TLR2, TLR4, TNF- $\alpha$ , IL-1, and NF- $\kappa$ B expression levels. *Biomed Pharmacother.* 2019;111:958-963.
  125. Vafaiepour Z, Ghasemzadeh Rahbardoar M, Hosseinzadeh H. Effect of saffron, black seed, and their main constituents on inflammatory cytokine response (mainly TNF- $\alpha$ ) and oxidative stress status: an aspect on pharmacological insights. *Naunyn Schmied Arch Pharmacol.* 2023;396(10):2241-2259.
  126. Saidin KS, Jais MR, Ismail EN, Ishak R. The effect of *Nigella sativa* and *Eucheuma cottonii* in collagen-induced arthritis mice. *Res J Pharm Technol.* 2020;13(3):1319-1323.
  127. Wahab S, Alsayari A. Potential pharmacological applications of *Nigella* seeds with a focus on *Nigella sativa* and its constituents against chronic inflammatory diseases: progress and future opportunities. *Plant.* 2023;12(22):3829.
  128. Pise HN, Padwal SL. Evaluation of anti-inflammatory activity of *Nigella sativa*: an experimental study. *Natl J Physiol Pharm Pharmacol.* 2017;7(6):707-711.
  129. Zakaria A, Jais MR, Ishak R. Analgesic properties of *Nigella sativa* and *Eucheuma cottonii* extracts. *J Nat Sci Biol Med.* 2018;9(1):23.
  130. Bashir MU, Qureshi HJ. Analgesic effect of *Nigella sativa* seeds extracts on experimentally induced pain in albino mice. *J Coll Phys Surg Pak.* 2010;20:464-467.
  131. Ahmad S, Abbasi HW, Shahid S, Gul S, Abbasi SW. Molecular docking, simulation and MM-PBSA studies of *Nigella sativa* compounds: a computational quest to identify potential natural antiviral for COVID-19 treatment. *J Biomol Struct Dynam.* 2020;39(12):4225-4233.
  132. Kooshki A, Tofighiyan T, Rastgoo N, Rakhshani MH, Miri M. Effect of *Nigella sativa* oil supplement on risk factors for cardiovascular diseases in patients with type 2 diabetes mellitus. *Phytother Res.* 2020;34(10):2706-2711.
  133. Siddiqui S, Upadhyay S, Ahmad R, et al. Virtual screening of phytoconstituents from miracle herb *Nigella sativa* targeting nucleocapsid protein and papain-like protease of SARS-CoV-2 for COVID-19 treatment. *J Biomol Struct Dyn.* 2020;40(9):3928-3948.
  134. Atif M, Naz F, Akhtar J, et al. From molecular pathology of COVID 19 to *Nigella sativum* as a treatment option: scientific evidence of its myth or reality. *Chin J Integr Med.* 2022;28(1):88-95.
  135. Ashraf S, Ashraf S, Ashraf M, et al. Honey and *Nigella sativa* against COVID-19 in Pakistan (HNS-COVID-PK): a multicenter placebo-controlled randomized clinical trial. *Phytother Res.* 2023;37(2):627-644.
  136. Chandra S, Murthy SN, Mondal D, Agrawal KC. Therapeutic effects of *Nigella sativa* on chronic HAART-induced hyperinsulinemia in rats. *Can J Physiol Pharmacol.* 2009;87(4):300-309.
  137. Onifade AA, Jewell AP, Adedeji WA. *Nigella sativa* concoction induced sustained seroreversion in HIV patient. *Afr J Tradit, Complementary Altern Med.* 2013;10(5):332.
  138. Onifade A, Jewell A, Okesina A. Seronegative conversion of an HIV positive subject treated with *Nigella sativa* and honey. *Afric J Infect Dis.* 2015;9(2):47-50.
  139. Khan RU, Jawad SM, Kiyani MM, Shah SA, Bashir S, Khan H. *Nigella sativa* extract abrogates traumatic brain injury-induced memory impairment in adult mice. *Heliyon.* 2024;10(18):e38106.
  140. Bin Sayeed MS, Shams T, Fahim Hossain S, et al. *Nigella sativa* L. seeds modulate mood, anxiety and cognition in healthy adolescent males. *J Ethnopharmacol.* 2014;152(1):156-162.
  141. Beheshti F, Hosseini M, Shafei MN, et al. The effects of *Nigella sativa* extract on hypothyroidism-associated learning and memory impairment during neonatal and juvenile growth in rats. *Nutr Neurosci.* 2017;20(1):49-59.
  142. Elibol B, Beker M, Terzioglu-Usak S, Dalli T, Kilic U. Thymoquinone administration ameliorates Alzheimer's disease-like phenotype by promoting cell survival in the hippocampus of amyloid beta<sub>1-42</sub> infused rat model. *Phytomedicine.* 2020;79:153324.
  143. Kadil Y, Filali H. *Nigella* fixed oil mitigates memory impairment in a rat aged model of cognitive decline, a pivotal role of BDNF and CREB signaling pathways in the hippocampus. *CNS Neurol Disord - Drug Targets.* 2022.
  144. Dalli T, Beker M, Terzioglu-Usak S, Akbas F, Elibol B. Thymoquinone activates MAPK pathway in hippocampus of streptozotocin-treated rat model. *Biomed Pharmacother.* 2018;99:391-401.
  145. Koshak A, Wei L, Koshak E, et al. *Nigella sativa* supplementation improves asthma control and biomarkers: a randomized, double-blind, placebo-controlled trial. *Phytother Res.* 2017;31(3):403-409.
  146. Tavakkoli A, Mahdian V, Razavi BM, Hosseinzadeh H. Review on clinical trials of black seed (*Nigella sativa*) and its active constituent, thymoquinone. *J Pharmacop.* 2017;20(3):179-193.
  147. Hoda F, Khanam A, Thareja M, Arshad M, Ahtar M, Najmi AK. Effect of *Nigella sativa* in improving blood glucose level in T2DM: systematic literature review of randomized control trials. *Drug Res.* 2023;73(01):17-22.
  148. Badar A, Kaatabi H, Bamosa A, et al. Effect of *Nigella sativa* supplementation over a one-year period on lipid levels, blood pressure and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: nonrandomized clinical trial. *Ann Saudi Med.* 2017;37(1):56-63.
  149. Badary OA, Al-Shabanah OA, Nagi MN, Al-Bekairi AM, Almazra MMA. Acute and subchronic toxicity of thymoquinone in mice. *Drug Dev Res.* 1998;44(2-3):56-61.
  150. Dollah MA, Parhizkar S, Latiff LA, Bin Hassan MH. Toxicity effect of *Nigella sativa* on the liver function of rats. *Adv Pharmaceut Bull.* 2013;3:97-102.
  151. Srivastava S, Bhargava A, Pathak N, Srivastava P. Production, characterization and antibacterial activity of silver nanoparticles produced by *Fusarium oxysporum* and monitoring of protein-ligand interaction through *in-silico* approaches. *Microb Pathog.* 2019;129:136-145.
  152. Rohini B, Akther T, Waseem M, Khan J, Kashif M, Hemalatha S. AgNPs from *Nigella sativa* control breast cancer: an in vitro study. *J Environ Pathol Toxicol Oncol.* 2019;38(2):185-194.
  153. Lin J, Gulbagca F, Aygun A, et al. Phyto-mediated synthesis of nanoparticles and their applications on hydrogen generation on NaBH<sub>4</sub>, biological activities and photodegradation on azo dyes: development of machine learning model. *Food Chem Toxicol.* 2022;163:112972.

154. Fragoon A, Li J, Zhu J, Zhao J. Biosynthesis of controllable size and shape gold nanoparticles by black seed (*Nigella sativa*) extract. *J Nanosci Nanotechnol.* 2012;12(3):2337-2345.
155. Dhandapani S, Xu X, Wang R, et al. Biosynthesis of gold nanoparticles using *Nigella sativa* and *Curtobacterium proimmune* K3 and evaluation of their anticancer activity. *Mater Sci Eng, A.* 2021;127:112214.
156. Chatterjee G, Saha AK, Khurshid S, Saha A. Comprehensive review of the antioxidant, antimicrobial, and therapeutic efficacies of black cumin (*Nigella sativa* L.) seed oil and its thymoquinone. *J Med Food.* 2025.
157. Alberts A, Moldoveanu E-T, Niculescu A-G, Grumezescu AM. *Nigella sativa*: a comprehensive review of its therapeutic potential, pharmacological properties, and clinical applications. *Int J Mol Sci.* 2024;25(24):13410.

**How to cite this article:** Pandey R, Pandey B, Bhargava A. An updated review on the phytochemistry and pharmacological activity of black cumin (*Nigella sativa* L.). *Adv Chin Med.* 2025;2(1):13-29. <https://doi.org/10.1002/acm4.33>