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REVIEW ARTICLE

NIGELLA SATIVA L.: A GOLDEN REMEDY: SIGNIFICANCE WORLDWIDE HIGHLIGHTING THEIR POSSIBLE USE FOR COVID-19

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Abstract

Nigella sativa L. is a therapeutic natural herb that cures several serious ailments, so can be considered a Golden remedy. It has been used for centuries and has a long history in different cultures. This review article has surveyed nearly all the relevant literature on *Nigella sativa* L. from 1960-2020, offering a broad range of data including the origin, taxonomy, botany, history of traditional uses in different regions then passing through their phytochemistry, pharmacology, and consumed natural pharmaceutical preparations till recent findings and their possible use in COVID-19 therapy. The main aim of this review is to focus on the importance of *Nigella sativa* L. as a medicinal herb used widely in therapy and to correlate its phytochemical constituents with their pharmacological effects. The biological importance was attributed to Thymoquinone in the first-place present in the volatile oil of the seeds and other classes such as sterols, triterpenes, tannins, flavonoids, and cardiac glycosides, alkaloids, saponins, coumarins, volatile bases, glucosinolates, and anthraquinones. Moreover, several studies confirmed its benefits in Alzheimer's disease, as a potent antioxidant, cytotoxic, antiallergic, antimicrobial, etc. In addition to other studies which documented the use of this plant mainly the seeds and the extracted essential oil, in the production of cosmeceutical preparations, and its role as a nutritive spice in the food industry due to its very low toxicity, besides their use as fodder for farm animals.

Keywords: Black cumin, essential oil, immuno-stimulant, *Nigella sativa* L., Ranunculaceae, Thymoquinone.

INTRODUCTION

Nigella sativa L. (known as Black cumin), one of the members of the Ranunculaceae family, is considered recently a "miraculous herb" for its broad pharmacological significance[1,2]. Because *N. sativa* L. is extensively dispersed over the world, it has been given several names based on its geographical location and language. It's known as the black seed, black cumin, black coriander, and black caraway in English-speaking areas. It is known as Kalaunji or Kalonji in India, Melanthion or Melaspermm in Greece, Granonero in Italy, and Al-Habbeh As-Sudah, Habbat Al-baraka or Kamun-Aswad in Arabic[3]. The traditional importance of *Nigella* seeds and their essential oil returns to their ability to cure several ailments. Many herbal preparations are used clinically worldwide including black cumin as one of its constituents mainly in Africa, Arabia, South, and Southeast Asia besides Mediterranean regions[1]. In many instances, *N. sativa* L. plays an important role in preventing and healing intoxication. Several studies have shown that *N. sativa* L. can reduce or eliminate the harmful side effects of a variety of medications, including various chemotherapeutics, analgesics, and antibiotics, as well as other substances including pesticides, organic solvents, and hazardous metals[4]. A volatile oil found in the seeds has insect repelling effects. *N. sativa* L. is used in museums to protect textiles, particularly linen, woolen materials, and paper-related artifacts, from insects and bacteria. Seeds can be strewn between the folds of linen and woolen clothing, as well as in the manuscript storage area, to safeguard the manuscript[5]. *N. sativa* L. seeds, powder, and volatile oil have recently been touted as a viable natural therapy that is effective against the SARS-CoV-2 virus and COVID-19 illness via many pathways. It has antiviral, antioxidant, anti-inflammatory, anticoagulant, immune-modulatory, bronchodilatory, antihistaminic, antitussive, antipyretic, and analgesic properties, and is utilized in the treatment of patients with COVID-19[6].

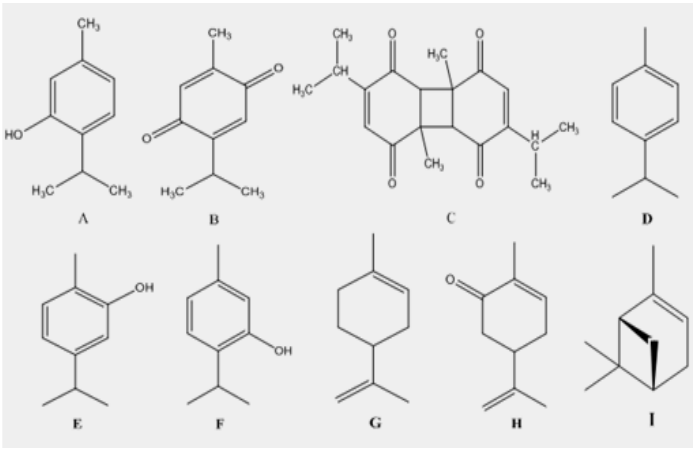

Figure 1: Chemical Structures of *N. sativa* L. volatile oil constituents:
Thymol (A), Thymoquinone (B) and Dithymoquinone (C), *p*- Cymene (D), Carvacrol (E), Thymol (F), Limonene (G), Carvone (H), α-pinene (I).

History of medicinal use

Nigella (fennel flower) is a tiny genus belonging to the Ranunculaceae (buttercup) family, with just approximately 15 species[7]. *Nigella* species are all annual plants with a brief life cycle that require open areas to proliferate. As a result, many of them may be found in artificial habitats. *N. sativa* L. (Black cumin) is the genus' most extensively spread and arguably best-known species, utilized as a condiment in addition to its medical value. Since the ancient age, this condiment has been propagated and grown for thousands of years. It is now a popular condiment throughout North Africa, the Arabian Peninsula, and the Indian subcontinent, as well as the focus of extensive pharmacological research and a dependable phytomedicine business[7]. The evolutionary origins of this genus are most probably in the center of species diversity, which occurs in the Aegean[7] and the adjacent Western-Irano-Turanian region[8]. *N. sativa* L. may thus have come into existence somewhere in this area, Also the great popularity that *N. sativa* L. has gained in pharmaceutical literature makes this review necessary due to the high amount of published literature generating the impression that the plant is of significant importance economically and medicinally or generally in the pharmaceutical industry.

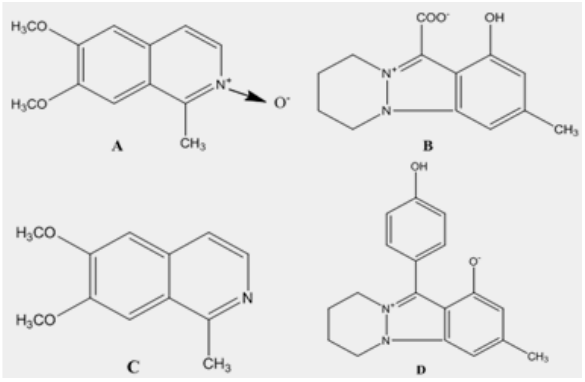

Figure 2: Structures of Alkaloids isolated from *N. sativa* seeds
Nigellimine N-oxide (A), Nigellicine(B), Nigellimine (C), Nigellidine (D).

Distribution and Taxonomic Consideration of *N. sativa* L.

The botanical classification of the plant according to the International Code of Nomenclature (ICN) for Algae, Fungi, and Plants[9] is documented to be as follows:

Kingdom: *Plantae*
Subkingdom: *Tracheobionta*
Superdivision: *Spermatophyta*
Phylum: *Magnoliophyta*
Class: *Magnoliopsida*
Order: *Ranunculales*
Family: *Ranunculaceae*
Genus: *Nigella*
Species: *sativa*[9]

Synonyms of *N. sativa* seeds L. includes *Nigella cretica* Mill., *Nigella truncata* Viv., *Nigella indica* Roxb. ex Flem[10], and common names includes Kalonji, Habat-ul-Sauda, Black Cumin, Black caraway, Black onion seed, Fennel Flower, Nutmeg Flower, Roman Coriander, Black seed, Damascena, Devil in-the-bush, Wild Onion Seed[1,11,12].

Genetic Issues

The genetic diversity of the *N. sativa* L. plant was investigated using random amplified polymorphic DNA (RAPD) markers, using samples taken from India, Pakistan, Saudi Arabia, Egypt, Oman, Syria, Tunisia, and Turkey.

It was discovered that genetic diversity varies greatly depending on the geographical source. This was ascribed to *N. sativa* L.'s capacity to adapt to various environmental factors in these areas. Genetically, the strains acquired from India and Pakistan were determined to be quite similar. Those from Egypt and Oman, on the other hand, were very different from those from India, Pakistan, Saudi Arabia, Syria, and Tunisia[13].

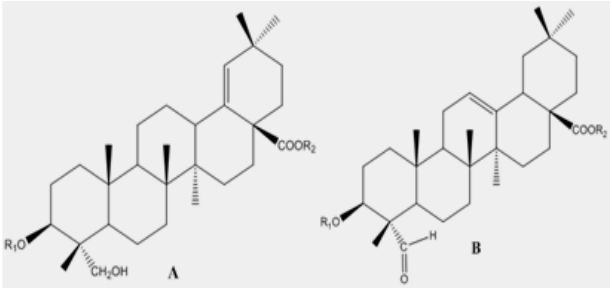

Figure 3: Two Triterpenoidal Saponins isolated from the seeds of *N. sativa* L.
Sativosides A and B; (A &B) A: R_1-*β*-D- Xyl (1→3)-*α*-L- Rha1 (1→2)-*α*-L-Ara, B: R_2-*α*-L-Rha II (1→4)-*β*-D- Glu II (1→6)-*β*-D-Glu I

PHYTOCHEMICAL CHARACTERISTICS

Monoterpenes make up the majority of *N. sativa* L.'s volatile oil, but following seed maturation, Thymoquinone becomes the most active element in the seeds and oil[14]. Only the seed coats contain volatile oil components as well as Nigellidine and Nigellicine alkaloids. Other compounds, such as dopamine, are located in the tissues of the inner seed, while other elements are scattered throughout the inner seed[14].

Volatile oil constituents

N. sativa L. volatile oil is a pale yellow liquid with a strong fragrant odor and flavor. Organic solvents such as ether, chloroform, and ethanol are readily soluble in the volatile oil, whereas water is sparsely soluble[15]. It is isolated by simple extraction with diethyl ether, then the organic solvent is evaporated under reduced pressure. The volatile oil content of *N. sativa* L. is about 0.4-0.5% w/w[15]. Besides, the Soxhlet extraction method of the seeds with petroleum ether can be carried out to yield35% of the volatile oil which on steam distillation yielded a higher amount of 1.5%[16]. The chemical constituents of the (Figure 1) are mainly monoterpenes including: *p*-cymene (2.8%), *α*-thujene (0.4%), Thymoquinone (6.1%), Carvacrol (traces), *α*-Longipinene (traces), Longifolene (0.6%), Thymohydroquinone (1.6 %), Palmitic acid, ethyl ester (traces), Linoleic acid methyl ester (0.5%), Linoleic acid, ethyl ester (traces), Oleic acid ethyl ester (traces), Oleic acid (traces), Linoleic acid (43%), Linoleic acid, butyl ester (5.7%), Oleic acid, butyl ester (4.5%), Glyceryl palmitate (1.6%), Glyceryl linoleate (21.9%). Besides, sterols as *β*- sitosterol.

Alkaloids

- The seeds of *N. sativa* L. contain 2 classes of alkaloids (Table 1, Figure 2); Isoquinoline alkaloids, such as Nigellidine[19], Nigellimine, and Indazole alkaloids as Nigellicine[20], Nigellimine-*N*-oxide [21].

Flavonoids

- Some flavonoids[22] were isolated and identified from the aerial parts of *N. sativa*L. as flaccidoside III, catechol, quercetin-3-gentiobioside, magnoflorine, nigelflavonoside B, nigelloside, quercetin sphorotrioside, kaempferol-3,7- diglucoside, kaemp-ferol 3-*O*-rutinoside, rutin. Also,quercetin-3-*O*-*α*- *L*-rhamnopyranoside 1, quercetin-7-*O*-*β*-*D*-gluco- pyranoside were identified[23].

Sterols

Sterols are listed in Table 1 are considered the main secondary metabolites of *N. sativa* L.[18] as Cholesterol, Campesterol, Campestanol, Stigmasterol, Sitosterol, Stigmastanol, Δ^5-avenasterol, Δ^7-stigmasterol, Δ^7-avenasterol, Lophenol, Obtusifoliol, 24-methyllophenol, Cycloeucalenol, Gramisterol, 24-ethyllophenol, Citrostadienol, Triucollol, Faraxerol, *β*-amyrin, Butyrospermol, Cycloartenol and 24- methylene cycloartanol

Triterpenoidal Saponins

Triterpenoidal saponins are the main class of saponins isolated from *N. sativa* L. (Table 1, Figure 3). Saponins isolated from the alcoholic extract of the seeds of *N. sativa* as Sativosides A and B [24], in addition to 3-*O*-[*α*-l-rhamnopyranosyl-(1→2)-*α*-*l*-arabino-pyranpsyl-hederagenin, 3*β*,23,28-trihydroxyolean-1-2-ene-3-*O*-*α*-*l*-arabinopyranoside(1→4)-*α*-rhamno-pyranosyl-(1→4)-*β*-*d*-glucopyranoside,3-*O*-*α*-*l*-rhamno-pyranosyl-(1→2)-*α*-*l*-arabino-pyranpsyl]-28-*O*-*β*-*d*-gluco-pyra-nosylhederagenin[22,25],3-*O*-[*β*-*d*-xylo-pyranosyl-(1→3)-*α*-*l*-rhamno-pyranosyl-(1→2)-*α*-*l*-arabino-pyranosyl]-hederagenin[26], Tauroside E, Sapindoside B[23].

Nutritive value of *N. sativa* L. seeds

Proteins (26.7%), lipids (28.5%), carbs (24.9%), crude fibres (8.4%), and total ash (8.4%) are all present in significant concentrations in the seeds of N. sativa L. (4.8%). Furthermore, the liver converts vitamins and minerals such as Cu, P, Zn, and Fe, as well as carotenes, into vitamin A, C, thiamine, niacin, pyridoxine, and folate[28,29]. Vanillic acid is said to be present in the roots and shoots.[28]. The seeds are also said to have a good quantity of fixed oil, which is high in saturated and unsaturated fatty acids. Saturated fatty acids include palmitic and stearic acids, which are generally found in amounts of 30% or less, whereas unsaturated fatty acids include linoleic acid (50-60%), oleic acid (20%), eico-dadienoic acid (3%), and di-homo-linoleic acid (10 %).

Table 1: Active constituents of different classes isolated from *N. sativa* L.

Chemical Group	Compound	References
Isoquinoline alkaloids	Nigellimine, Nigellimine-*N*-oxide	21
Indazole alkaloids	Nigellidine, Nigellicine	19
Acids	Stearic acid, Linoleic acid, Palmitic acid, Oleic acid, Arachidic acid, Eicosadienoic acid.	22
Sterols	Cholesterol, Campesterol, Campestanol, Stigmasterol, Sitosterol, Stigmastanol, Δ^7-avenasterol, Δ^7-stigmasterol, Δ^7-avenasterol, Lophenol, Obtusifoliol,24-methyllophenol, Cycloeucale-nol, Gramisterol, 24-ethyllophenol, Citrostadienol, Triucollol, Faraxerol, *β*-amyrin, Butyrospermol, Cycloartenol,24-methylene cycloartanol	18,27
Triterpenoidal Saponins	α- hederin, Sativosides A and B 3-*O*-[*α*-l-rhamnopyranosyl-(1→2)-*α*-l-arabino-pyranosyl-hederagenin 3*β*,23,28-trihydroxyolean1-2-ene-3-*O*-*α*-l-arabinopyranoside (1→4) -*α*-rhamnopyranosyl-(1→4)-*β*-*d*-glucopyranoside, 3-*O*-*α*-l-rhamnopyranosyl-(1→2)-*α*-l-arabinopyranpsyl]-28-*O*-*β*-*d*-glucopyranosyl-hederagenin Tauroside E, Sapindoside B	24
Flavonoids	flaccidoside III, catechol, quercetin-3-gentiobioside, magnoflorine, nigelflavonoside B, nigelloside, quercetin sphorotrioside, kaempferol-3,7-diglucoside, kaempferol 3-*O*-rutinoside, rutin. Also, quercetin-3-*O*-*α*-*L*-rhamnopyranoside 1, quercetin-7-*O*-*β*-*D*-gluco- pyranoside	22

Biological activities of extracts confirmed by scientific research

The applications of *N. sativa* L. confirmed by scientific experiments and the pharmacological action profile of this species highly recommended in modern phytotherapy are summarised in Table 2 with their suggested mechanism of action.

Natural preparations containing *N. sativa* L. and their uses

The combination of *N. sativa* L. ointment and the oral administration of the crude powder of the seeds exhibited effective anti-psoriatic activity [61].

Pharmaceutical Preparations including *N. sativa* L. and TQ

Thymoquinone is the main ingredient of *N. sativa* L. essential oil; it is of limited use in therapy due to its poor water solubility, high instability in aqueous solution, and pharmacokinetic drawbacks. TQ was combined with polymeric solubilizers for developing polymeric micelles which led to a bio-enhancement[66].

***N. sativa* L. seeds in veterinary medicine**

Because *N. sativa* L. seeds and oil are included as a healthful and nutritious component in farm animal formulations, supplementation with *N. sativa* L. has a good effect on animal production metrics. Because of its therapeutic characteristics, *N. sativa* L. is used in animal feed. It is an excellent source of proteins, carbs, fatty acids, and a range of bioactive components. *N. sativa* L. is a versatile plant with many applications. Broiler chickens, laying hens, rabbits, ruminants, and pseudo-ruminants' feed consumption, mortality rate, digestibility, active and reproductive performances, milk yield and composition, egg compositional characteristics, blood chemistry parameters, health status, and carcass traits are all improved by *N. sativa* L[67]. Another study found that supplementing broiler diets with black cumin seeds (1%) increased body weight, feed conversion ratio, and carcass yield after a 6-week growing span, suggesting that *N. sativa* L. (1%) may be used as a natural growth promoter material in broiler diets[68]. *N. sativa* L. had a major impact on growing lambs as well, and growth efficiency parameters when fed to growing lambs[69]. *N. sativa* L. seeds in a study on 40-week-old White-Leghorn birds, significantly improved egg yield, egg mass, and eggshell thickness[70].

Drug interactions and toxicity

Many human clinical studies stated that the simultaneous administration of *N. sativa* L. extracts and/or its essential oil with the conventional treating drug improved its activity and declined significantly its side effects. Many studies revealed the protective effect of *N. sativa* L. and intoxication activity against different chemical agents[4,71]. It possesses ameliorative effects against several drugs intoxication as[71]. Chemical war victims from mustard gas inhalation taking *N. sativa* L. extract required less salbutamol and corticosteroids[72]. Asthma patients using *N. sativa* L. decoction decreased the use of all the treating drugs as inhaled corticosteroids: beclomethasone or fluticasone inhalers and theophylline, and beta-agonists[73]. In another study, the use of *N. sativa* L. seeds helped in reducing acute opiate withdrawal symptoms, craving, and relapses through an open study including 50 persons addicted to opioids. This study continued for 12 weeks with a daily dose of *N sativa* L. seeds of 250-500 mg 3 times[74]. Some clinical studies were carried out one of which was on 40 females suffering from rheumatoid arthritis using anti-rheumatic drugs such as methotrexate, hydroxychloroquine, diclofenac.

Table 2: Pharmacological profile of *N. sativa* L. seeds and their suggested mechanism.

Activity	Mechanism of action	Compounds Supposed to be Responsible	Doses/dose range	Ref.
	***Ex-vivo* study**			
Allergic Diarrhea	- inhibition of the cyclooxygenase and 5- lipoxidase pathways. - regulation of the toll-like receptor 4/NF êB pathway.	Thymoquinone	30 mg/kg body weight	30
	***In-vivo* study**			
Allergic Rhinitis	- reduced the level of allergen-induced lung remodeling which proved to have a strong therapeutic effect.	Black seed oil	4 ml/kg body weight	31
Alzheimer's disease	- ↓ TBARS & 5-LOX levels - ↑ GSH extent and SOD action - Causes disaggregation of Aβ peptide - prevents the decline of neurons - Slows	Thymoquinone	0.8 mg/kg	32
Analgesic	- inhibition of lipo-oxygenase and/or cyclo-oxygenases	Thymoquinone	25 mg/kg, 50 mg/kg	33
Anti-cancer	- inhibition of cell proliferation, apoptosis induction through dependent-pathway and P53 independent, antioxidant activity, and glutathione alternation.	Thymoquinone Saponins α-hederin	2 ml of aqueous extract	34-37
Diuretic	- natriuretic and kaluretic effect	Black seed oil Thymoquinone	100 mg/kg	38
Immunomo-dulatory/ Immuno-protective	- increasing macrophage activity and lymphocyte numbers. - Inhibition of inflammatory processes. - strengthening the immune response, especially in T cells.	Thymoquinone α-linoleic acid Stearic acid	5mg/kg	39-42
	Clinical Trials			
Anti-hyperlipidemic	- regulate cholesterol synthesis through regulation of HMG-CoA reductase, Apo-A1, Apo-B100, and LDL-receptor genes; enhancing the efficiency of liver cells to remove LDL from the blood circulation; also contributing to decreasing dietary cholesterol absorption, and increasing the primary bile synthesis.	Thymoquinone migellamine flavanoids sterols soluble fiber (mucilage) polyunsaturated fatty acids	50 and 100 mg/kg	43-45
Asthma/broncho dilatory	- increase in peak expiratory flow (PEF), forced expiratory volume in one second (FEV1), maximal expiratory flow (MEF), maximal mid expiratory flow (MMEF), and specific airway conductance.	Black seed oil Thymoquinone	50 and 100 mg/kg	46
Hepato-protective	- antioxidant activity	Black seed oil Thymoquinone	--	39
Pancreatic carcinoma	- Inhibition of cell growth in cancer cell lines	Thymoquinone	--	39
Arthritis	- anti-inflammatory processes by preventing the production of eicosanoids such as thromboxane B2 and leukotriene B4 via suppressing COX and 5-lipoxygenase in addition it inhibits the leukotriene C4 synthase activity	Thymoquinone	--	39,47-49
Reproductive system	- Prevention of cell death and loss of tissue weight or volume of sexual cells by inhibiting cyclooxygenase and lipo-oxygenase enzymes and reducing the harmful effects of free radicals.	Black seed oil Thymoquinone	0.5 and 1.5 g/Kg	50,51
Wound healing activity	- Enhancing the proliferation of fibroblasts and promoting the level of beta-FGF.	Thymoquinone		52
	***In vitro* study**			
Anti-diabetic	- regulating liver enzymes activity associated with glucose metabolism. - reducing gluconeogenesis. - antioxidant activity; preservation. - the proliferation of pancreatic beta cells. activating adenosine monophosphate kinase.	Thymoquinone	200 µg of chloroform fraction	22,53-55
Anti-inflammatory	- indirect activation of the supraspinal mu (1)- and kappa-opioid receptor subtypes	Thymoquinone Saponins	5, 10, 50, and 100 µg/mL	24,39, 56,57

Cont…

Anti-microbial activity	- the presence of active compounds with anti-microbial activity	Thymoquinone Thymohydroquinone melanin	Volatile oil	58,59
Antioxidant	improve scopolamine-induced cognitive impairment and reduced the AChE activity and oxidative stress of the rat's brain	Phenolic compounds	200 µg of chloroform fraction	22,60-62
Anti-ulcer	-	Black seed oil Thymoquinone	-	39
Anthelmintic	- decrease in glutathione-S-transferase and superoxide dismutase activity and reduced glutathione (GSH) level -inhibition of Cathepsin L (Cat L) gene expression in thymoquinone treated worms.	Thymoquinone	60 µM conc.	57,63
Cytotoxic	- Inhibition of cell growth in cancer cell lines: MCF7	Black seed oil Thymoquinone	IC_{50} values of 14.25 ± 0.84 and 8.05 ± 0.22 µg/ml	64
Neuroprotective	- substantial anti-inflammatory and antioxidant potential	Thymoquinone	0.1-1 µM	65

It was revealed that when *N. sativa* L. seeds oil was administered as an adjuvant therapy a significant decrease in the disease score and less morning stiffness occurred[75]. In a 21 patients study with non-ulcer *Helicobacter pylori*, dyspepsia taking 2 grams of seed powder in combination with omeprazole daily for 4 weeks was significantly effective in eradicating the *H. pylori* in 66.7%[76]. On the contrary, *N. sativa* L. extract-phenobarbitone combination must be avoided as concomitant use of the herb during treatment with phenobarbitone showed undesirable drug interactions[77]. Moreover, several i*n- vitro* and *in-silico* studies were carried out on the effect of *N. sativa* L. and volatile oil constituents in the presence of certain drugs. An *in vitro* study on the anticancer effect of Oxaliplatin and/or Gemcitabine against pancreatic cancer which increased significantly after adding 3 mg thymoquinone reducing local invasion and nodal metastasis reduced pancreatic cancer cell growth[78]. The use of Gentamicin with 50 mg/L thymoquinone in drinking water for 8 days completely reversed its kidney toxicity and the increase in serum creatinine, BUN, TBARs, and total nitrate/nitrate and decreases in kidney glutathione, glutathione peroxidase, catalase, and ATP levels in rats[79]. Doxorubicin-induced cardiotoxicity was indicated by the increase in serum lactate dehydrogenase and creatine phosphokinase levels phosphokinase was prevented with 5 days of pretreatment and 2 days of parallel treatment with 10 mg/kg daily of thymoquinone in rats. This protection is due to the *in vitro* superoxide radical scavenger potency and inhibition of lipid peroxidation possessed by thymoquinone[80]. The hepatotoxicity caused by acetaminophen was prevented by 5 days of 2 mg/kg/day of thymoquinone in mice. This *in vitro* study was carried out by measuring the level of certain liver enzymes which returned to the normal levels upon the addition of Thymoquinone in therapy[81]. When the seed oil was given at 880 mg/kg for 2 weeks before a 1 ml dose of ethanol, it significantly reduced the formation of stomach ulcers by increasing mucosal glutathione levels and mucin and decreasing mucosal histamine in rats[82]. Thymoquinone given at 20 mg/kg reduced ethanol-induced stomach ulcers and the associated lipid peroxidation and glutathione depletion in rats[83].

Furthermore, *N. sativa* L. and its main constituent Thymoquinone could protect some tissues against most drug overdoses including analgesics, anti-cancer, immune-suppressive, antibiotics, antiretrovirals, and anti-seizures [71]. Several mechanisms are involved in *N. sativa* L. antidotal effects including antioxidant, anti-inflammatory, free radical scavenging, improvement in the disturbing levels of biochemical markers, modulation of antioxidant defense systems, inhibition of apoptosis, and regulatory effects on genes expression, and different signaling pathways[71].

N. sativa L. and COVID-19

N. sativa L. was reported to have antiviral activity either separately or in combination with other herbs. A herbal preparation that consists of Extracts of (*Anthemis hyaline* DC., *N. sativa* L., and *Citrus sinensis* (L.) Osbeck) was found to decrease the replication of CoV virus, as it increased IL-8 level, expression of the genes TRPA1, TRPC4, TRPM6, TRPM7, TRPM8, and TRPV4 changed significantly[84]. Several studies recommended *N. sativa* L. as an adjuvant therapy with repurposed drugs including Chloroquine, Hydroxychloroquine, Remdesivir, and Favipiravir used to manage patients with COVID-19[46].Various randomized controlled trials, case reports, pilot studies, and *in vitro* and *in vivo* investigations confirmed that *N. sativa* L. possesses antiviral, antioxidant, anti-inflammatory, immunomodulatory, bronchodilatory, anti-histaminic, anti-tussive activities related to Coronavirus and signs of COVID-19[46].

The main active constituents revealed *in silico* affinity with SARS-CoV-2 enzymes and proteins. They possess high to moderate affinities where they potentially inhibit SARS-CoV-2 replication and attachment to host cell receptors. These constituents include nigelledine, *α*-hederin, hederagenin, thymo-hydroquinone, and thymoquinone[85]. Besides, Nigellidine and α-hederin have been identified as a potential inhibitors of SARS CoV-2[6].

CONCLUSION

Finally, *N. sativa* L. may be used as an adjuvant treatment alongside repurposed chemical drugs for the treatment of COVID-19, which nearly diminishes the side effects of other medications by lowering their doses. However, further randomized controlled trials are required to validate the potential and benefits of *N. sativa* L. seeds and essential oil as an alternative herbal therapy for SARS CoV-2.

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AUTHOR'S CONTRIBUTION

Fayed MAA: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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