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Nigella sativa L. as a Potential Natural Product for the Treatment of COVID-19

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Abstract

The world is now facing a public health emergency caused by the coronavirus pandemic (COVID-19). The World Health Organization (WHO) has called it an emerging pandemic due to its sudden appearance and distribution. Coronavirus disease 2019 (COVID-19) is a pandemic caused by the Coronavirus2 of the Extreme Acute Respiratory Syndrome (SARS-CoV2). *Nigella sativa* (*N. sativa*) (Family Ranunculaceae) is a globally used medicinal herb. Unani and Tibb, Ayurveda, and Siddha are only a few of the western medical systems that use it. *N. sativa*, also known as black seed, is an essential medicinal plant that has long been used as a multipurpose medicinal agent in various countries. Immune deficiency, autophagy deficiency, oxidative stress, pathological inflammation, diabetes, cardiovascular diseases, and bacterial and viral infections are all treated effectively with the essential oil and other preparations of the *N. sativa* crop. It comprises of many essential groups of bioactive compounds, one of which, thymoquinone, has piqued the scientific community's interest due to its active function in treating a wide variety of diseases. The therapeutic effectiveness of *N. sativa*, as well as recent computational results, clearly suggest that it may be used to tackle the COVID-19 pandemic that has recently arisen. The aim of this review is to highlight the therapeutic importance of *N. sativa* in conventional medicine, as well as the potential for its use as an antiviral agent against the SARS-CoV2 virus and for further preclinical research.

Keywords: COVID-19; SARS-CoV2; *Nigella sativa*; natural products; World Health Organization; pandemic.

1. Introduction

Aside from their function in ecosystem maintenance, plants are considered natural sources of heat, feed, and medicinal compounds. Since humans are often confronted with various illnesses, accurate detection of healing agents and subsequent care recommendations are critical for maintaining a stable workforce [1]. Several plants contain active biomolecules that have been shown or may have the ability to be therapeutic. The use of plant resources to cure numerous human diseases has been practiced since ancient times [2].

Just a few plant species have been extensively studied for their medicinal properties, ability, mechanism of action, safety assessment, and toxicological studies, so many researchers are focused on medicinal plants. Since several studies discovered its broad range of pharmacological promise, *Nigella sativa* (*N. sativa*) (Family Ranunculaceae) is emerging as a wonder herb with a rich historical and religious history (Figure 1). Black seed [3,4] is the generic name for *N. sativa*, is a plant native to Southern Europe, North Africa, and

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Southwest Asia that is grown in a variety of countries around the world, including the Middle Eastern Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, and Saudi Arabia [4].

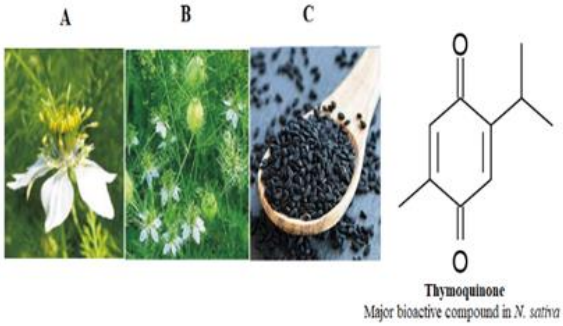

Fig. 1 *Nigella sativa* (A: flower, B: whole plant, C: and seeds), and the chemical structure of the major bioactive compound (Thymoquinone), which is a significant bioactive constituent making up 30–48% of the total compounds, in *N. sativa* [5].

N. sativa seeds and oil have been used to cure a variety of illnesses all around the world for decades. It is also a main ingredient in Unani and Ayurveda, two Indian classical medicinal systems [3,6]. Since it was mentioned in one of the Prophetic hadith that black seed is the cure for all diseases except death, it is regarded as one of the most effective types of healing medicine available among Muslims. Tibbe-Nabwi (Prophetic Medicine) [7] also recommends using it on daily basis.

N. sativa has been extensively studied for its biological activities and therapeutic potential, including diuretic, antihypertensive, antidiabetic, anticancer, and immunomodulatory, analgesic, antimicrobial, anthelmintics, analgesics, and anti-inflammatory, spasmolytic, bronchodilator, gastroprotective, hepatoprotective, renal secure, and antioxidant. *N. sativa* seeds are commonly used to cure illnesses such as bronchitis, asthma, diarrhea, rheumatism, and skin disorders (Figure 2). It is also used as a liver tonic, digestive aid, antidiarrheal, appetite stimulant, emmenagogue to improve milk production in breastfeeding mothers, to prevent parasitic infections, and to strengthen the immune system [3,8-11]. Furthermore, volatile oils and alkaloids are often concerned with biological activities within the different ingredients of *N. sativa* crop.
Nigellone, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, and -pinene, d-limonene, d-citronellol, p-cymene, carvacrol, t-anethole, 4-terpineol, and longifolene are some of the volatile oil's major constituents [3]. Isoquinoline (nigellicimine, nigellicimine n-oxide) and pyrazol (nigellidine and nigellicine) are two alkaloids that stand out from the others [12]. Among the various active constituents identified thus far, thymoquinone is the most important bioactive principle, with antioxidant [13], anti-inflammatory [14], anti-cancer [15], antibacterial [16], antifungal [17], and anticonvulsant [18] properties. Black seed has been shown to have immunomodulatory properties [19]. In addition, some experiments have found that the black seed has antiviral properties [20]. Since the latter have a low degree of toxicity, they are also used in food as a flavoring agent in breads and pickles [3,21].

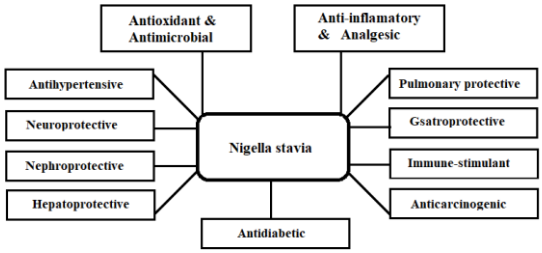

Fig. 2 Several medicinal properties of *N. sativa* (black cumin seeds).

Greater efforts are required to transform the herbal and local medical systems and leverage the plant in modern medicines, particularly in the light of its health promotion and disease control activities. As a result, you will be able to get the best benefit of black seeds. A molecular docking research recently described nigellidine and α-hederin as novel inhibitors of SARS-CoV-2 among *N. sativa* compounds [22]. Even a common practice of using black seed formula and steam to alleviate the effects of the disease has been discovered to be successful.

This evidence clearly indicates that *N. sativa* seed and its active constituents have anti-COVID-19 therapeutic potential. The aim of this review is to include an overview on the therapeutic properties of *N. sativa* in conventional medicine schemes, as well as possibilities for modern medicine use. We recommend that plant-derived drugs may be used as an option to deal with SARS-CoV-2 in this review. We revisited the pharmacological potentials of *N. sativa* seed and its bioactive to achieve a clearer understanding of the therapeutic benefits, and we offer a detailed review of these natural products' possibilities for the prevention and cure of COVID-19. The key aim of our new initiative is to see whether there is any other way to avoid this devastating pandemic.

2. N. sativa Effect on Health

Traditional medicinal systems have used black cumin (*Nigeria sativa*) to cure several ailments. *N. sativa* is

an herb that is used to treat diabetes mellitus in Moroccan folk medicine. The effectiveness of the seed oil, essential oil, and the isolated primary constituent thymoquinone (TQ) has been studied in several preclinical and clinical trials. These findings justify its use in asthma, allergic rhinitis, and atopic dermatitis, according to the researchers. Dyspepsia, respiratory disorders, asthma, and metabolic syndrome can all benefit from black cumin [23,24]. According to a meta-analysis of clinical trials, *N. sativa* can lower systolic and diastolic blood pressure in the short term, and its multiple extracts can lower triglycerides, LDL, and total cholesterol. Several studies undertaken over the last decade have confirmed its health benefits, especially in the areas of diabetes, dyslipidemia, hypertension, and obesity. A detailed examination of all human trials has shown that it can benefit from Sativa supplementation for glycemic regulation [25].

3. COVID-19, and the Possibility of Intervention Seeds of *N. sativa*

The health-beneficial effects of *N. sativa* seed and its main active compound, thymoquinone, on multiple body functions, including the immune system, have been studied extensively over the last two decades. However, the exact mechanism by which *N. sativa* can mediate protective effects against viral infection is still unknown. The parts that follow summarize what is currently known about *N. sativa's* role in mediating defence against SARS-CoV-2-associated pathological factors such as immune dysfunction, autophagy dysfunction, oxidative stress, inflammation, and co-morbidities including diabetes, hyperglycaemia, cardiovascular diseases, and bacterial and viral infection [26] (Table 1).

N. sativa's antiviral actions on multiple viruses have been documented in *in vitro* studies [42]. For instance, infected mice with murine cytomegalovirus had their viral load lowered to undetectable thresholds following treatment with *N. sativa* oil [43,44]. HIV-1 replication has been shown to be inhibited by *N. sativa* honey [44]. Herpes simplex and hepatitis A virus infections were virucidal when *N. sativa* was used. With induced interleukin 8 secretion and downregulation of transient receptor potential (TRP) genes such as TRPM6, TRPA1, TRPC4, and TRPM7, *N. sativa* lowered the coronavirus load in infected HeLa cells [43,45].

Koshak & Koshak (2020) [43] reported a case study where a six-month therapy with *N. sativa* resulted in prolonged seroreversion in a 46-year-old HIV patient, and six additional HIV cases were identified. In recent years, computational screening approaches for evaluating natural product therapeutic potential have been enabled by *in silico* molecular docking studies. These studies make use of bioinformatics tools to figure out how candidate drugs affect therapeutic activity by modeling drug-protein interactions and examining the impact on biological pathways and functions [43,46].

There were at least eight *in silico* experiments that investigated the effects of *N. sativa* compounds on SARS-CoV-2 in the literature review published by Koshak & Koshak (2020) [43] for the years 1990 - 2020, using electronic databases. The latter provides a description of those findings (Table not provided herein). However, no clinical trials on *N. sativa* in human coronavirus cases have been published yet. The binding affinity of compounds from *N. sativa* and certain antiviral drugs with SARS-CoV-2–related molecular targets including main proteases, main peptidase, angiotensin converting enzyme 2 (ACE2), and heat shock protein A5 was determined using molecular docking. Any natural compounds can prevent coronavirus from adhering to host epithelial cells [43]. Nigelledine, an alkaloid present in *N. sativa*, had an energy complex score that was comparable to chloroquine and higher than hydroxychloroquine and favipiravir when docked with 6LU7 active sites (Figure 3). α-Hederin, a saponin found in *N. sativa*, outperformed chloroquine, hydroxychloroquine, and favipiravir when docked with 2GTB active sites in terms of capacity (Figure 3) [43,47]. As a result, natural compounds present in *N. sativa*, such as nigellidine, α-hederin, hederagenin, thymohydroquinone, and thymoquinone, were found to be potentially active inhibitors of coronavirus. To establish the efficacy of *N. sativa* against coronavirus, preclinical evidence is needed. If preclinical trials indicate that *N. sativa* has clinical efficacy, a clinical Phase I trial in patients with COVID-19 is proposed to further examine its clinical potential.

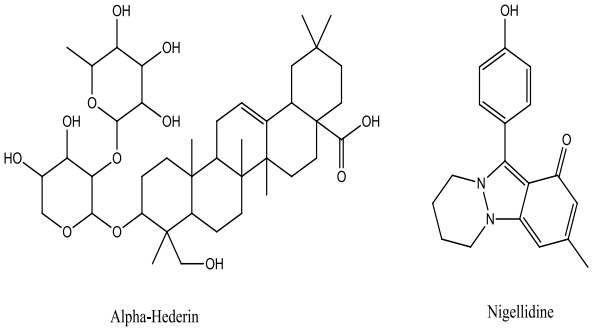

Fig. 3 The chemical structures of the alpha-Hederin (saponin) and Nigelledine (alkaloid) present in *Nigella sativa.*

Table 1. **Pharmaceutical effects of *N. sativa* on various pathophysiological conditions.**

Model used and intervention(s)	Therapeutic Effects of *N. sativa* or its active components	Mechanism	Ref. #
TQ (2.5 & 5 mg/kg) was given to mice with lipopolysaccharide-induced AD for 7 days	Alzheimer's disease	(i) ↓ TBARS & 5-LOX levels, (ii) ↑ GSH extent and SOD action (iii) Affects disaggregation of Aβ peptide (iv) inhibits decreasing of neurons (v) Reduces the rate at which cognitive abilities deteriorate	[27]
To investigate 1-methyl-4-phenylpyridinium (MPP+) and rotenone-induced neurotoxicity in a PD model, cultures were given TQ (0.01, 0.1, 1, and 10 M) on day 8 for four days	Parkinson's disease	(i) Dopaminergic neurons were rescued by (ii) Its antioxidant and anti-inflammatory effects	[28]
Guinea-pigs *N. Sativa* seed hydroethanolic extract (0.125 mg/mL and 0.25 mg/mL)	Lung & trachea	(i) Increases anti-inflammatory activity while improving tracheal responsiveness (ii) Lowering histamine delivery	[29]
For a period of four weeks, stressed and unstressed mice (10 and 20 mg/kg of TQ) were given 10 and 20 mg/kg of TQ.	Depression & anxiety	(i) without affecting levels of nitrite (ii) ↑ GABA content (20 mg/Kg). Stressed mice: (20 mg/kg revealed anxiolytic impacts with: (i) ↓ plasma nitrite level (ii) Reversal of the reduced GABA	[30]
TQ as supplementary treatment for 4 weeks in a double-blind placebo-controlled randomized control study in refractory epilepsy	Epilepsy	(i) Seizure frequency has decreased significantly (Those who received combination therapy)	[31]
Peritoneal Wistar rat mast cells.	Anti‑ inflammatory agent in asthma	(i) *N. Sativa* ethanol extract effectively inhibit histamine release from peritoneal Wistar rat mast cells proportionally to its concentration. (ii) It is effective as an anti-inflammation on mast cells by inhibition of histamine release and has no toxic effect on mast cell.	[32]
Mice after subcutaneous injection	Anti-bacterial activity	(i) Plant remedies would be more effective if they were combined with antibacterial medicines (i) *Staphylococcus aureus* infection in mice was eliminated by ether extract	[33]
Mice	Anti-fungal activity	(i) A five-fold reduction in kidney candida (ii) 8-fold reduction of candida in the liver (iii) Candida in the spleen has decreased 11-fold	[34]
Mice	Anti-schistosomal activity	(i) In mice, it prevented most of the hematological and biochemical alterations associated with schistosomiasis (ii) Mice with schistosomiasis had their antioxidant capacity improved	[35]
Mice	Antioxidant activity	(i) The capacity of total antioxidants has risen (ii) Malondialdehyde and NO levels in the blood and tissues reduced	[36]
Menopausal women	Anti-hyperlipidemic activity	(i) Total cholesterol, low density lipoprotein cholesterol, and triglyceride levels all dropped (ii) High-density lipoprotein cholesterol levels have increased	[11]
Balb/c mice	Anti-cancer activity	(i) The toxicity and ultrastructural alterations caused by CCl_4 dosages were reduced	[37]
Streptozotocin-diabetic rats	Anti-diabetic activity	(i) The amount of glucose in the blood was reduced when it was elevated (ii) Reduced blood insulin levels and enhanced partial regeneration/proliferation of pancreatic cells (iii) The amount of MDA in the tissues and the amount of glucose in the blood were both reduced (iv) The amount of SOD in the tissues and the amount of insulin in the blood increased	[38]
Shay rats	Cardiovascular protective activity	(i) In pylorus-ligated Shay rats, it improved ulcer severity and baseline stomach acid production (ii) The ethanol-induced depletion of gastric mucus content and non-protein sulfhydryl concentration in the stomach mucosa was replenished	[39]
Wistar rats	Gastro-protective activity	(i) LDH, GSH, and SOD levels were normalized (ii) Lipid peroxide levels have been restored to their previous levels (iii) In large dosages, the GSH content decreased	[40]
Wistar rats	Nephro-protective activity	(i) Malondialdehyde levels in the liver and erythrocytes reduced (ii) The levels of glutathione, glutathione peroxidase, superoxide dismutase, and catalase all dropped	[41]

Key to abbreviations:
TBARs: Thiobarbituric acid reactive substances, **GABA**: gamma amino butyric acid, **MDA**: malondialdehyde, **DA**: dopamine, **GSH**: glutathione peroxidase, **SOD**: superoxide dismutase, **TQ**: thymoquinone, **Aβ**: beta amyloid peptides, ↑: increase, ↓: decrease

Additionally, the ability of *N. sativa* (black cumin seeds) to treat COVID-19 patients was investigated in this review, as Prophet Muhammad (PBUH) said, "There is a cure for any disease but death in the black cumin." Furthermore, the black cumin is identified as "Curative black seed" in the Holy Bible and as "Melanthion of Hippocrates and Dioscorides" and "Glitch of Pliny" [48,49].

N. sativa is a possible herbal candidate for treating COVID-19 patients since it has antiviral, antioxidant, anti-inflammatory,anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic, and analgesic properties. Furthermore, *N. sativa* has been shown to have antihypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic, anti-ulcer, and antineoplastic properties, all of which may benefit COVID-19 patients with comorbid conditions [49,50]. In addition, active constituents of *N. sativa*, such as nigellidine and α-hederin, have been identified as possible SARS CoV-2 inhibitors [49].

4. COVID-19 Prevention at the Present Time

To stop the latest pandemic from spreading further and to avoid potential relapses, successful protection is urgently needed. At this stage, vaccination, convalescent serum, monoclonal antibodies, and readily available antiviral drugs are the most promising alternatives. Several candidates stand out as current front runners in the global race to produce a vaccine solution against SARS-COV-2, with the aim of deploying by the end of 2020. Although vaccine research continues apace, conventional medicinal strategies would need to be repurposed or reinvented to fulfill the challenge. Repurposing could speed up care choices without jeopardizing strict public health requirements, thanks to a proven safety record and optimized mass production infrastructure. Repurposing preventative care, or prophylactics, may mitigate viral exposure for the public and giving health authorities more control of the epidemic by filling the reaction gap between treatment and the forthcoming vaccine. Several substances of note are illustrated, as well as those that are currently undergoing clinical trials [51].

Majeed *et al*., 2020 [1], reported that *N. sativa* is a possible medicinal source for a variety of diseases due to the inclusion of pharmaceutically essential constituents including thymoquinone, thymol, and nigellone. Antianalgesic, anti-inflammatory, wound curing, anti-oxidative, anti-asthmatic, corrective-rheumatoid arthritis, and immune-stimulant effects have been reported for its extracts, milk, and supplementation [1,52]. Animal tests [53] have demonstrated that *N. sativa* extracts and oil have positive effects on obesity, lipid profile, and insulin control. The anti-ulcerative potential of *N. sativa* was confirmed in rats by Al Mofleh et al. [54]. Additionally, in rats, Parhizkar *et al*. [55] observed that *N. sativa* increased menstruation and the post-menopause stage. Moreover, *N. sativa* increased kidney function and protected rats from cytotoxicity in a five-week study [56]. Other research [1,56,57] have shown that black seed has defensive properties against neurotoxicity, hepatic damage, fatty liver, colon cancer, and gastrointestinal disorders.

5. Natural Compounds' Potential for COVID-19 Clinical Therapy

Xian *et al*., 2020 [58], reported that when the virus enters the host cell, its positive genomic RNA attaches directly to the ribosome, triggering the translation of two large, coterminal polyproteins, which are then converted into components for packaging new virions through proteolysis. Two proteases involved in the progression of proteolysis are 3CLpro and PLpro. The CoV code for the RdRp replicase, which replicates the RNA genome. These four proteins are responsible for a virus's pathogenicity. Therapeutics targeting spike, RdRp, 3CLpro, and PLpro can all be used to treat SARS-CoV-2 [58,59].

Furthermore, tentative studies of COVID-19 patient genomic sequences reveal that the catalytic sites of the four COVID-19 enzymes that may be antiviral targets are strongly conserved and share a high degree of sequence similarity with the corresponding SARS and MERS enzymes. SARS-CoV-2 and SARS-CoV share 82% sequence identity and over 90% sequence identity in many essential enzymes [58,60]. As a result, repurposing current MERS and SARS inhibitors for COVID-19 therapy is a reasonable option [59]. Xian *et al*., 2020 [58], found that natural compounds like theaflavin and cepharanthine suppressed SARS-CoV-2 by suppressing RdRp and ACE activities; hirsutenone and tanshinones I-VII inhibited PLpro activity, while celastrol, pristimererin, tingenone, iguesterin, chalcones I-IX, and quercetin-3-β-galactoside. Since SARS-CoV and SARSCoV-2 are so similar, both natural compounds and their original plants with antiviral activities against SARS-CoV and MERS-CoV could potentially defend against COVID-19.

6. COVID 2019 Treatment Choices

COVID-19 has been cured using several therapeutic approaches. Natural and synthetic therapies are the most widely discussed of the different treatments.

6.1. Natural Treatment

The natural cure is a naturally occurring secondary metabolite with antiviral properties isolated from living species such as plants, animals, fungi, and bacteria [61,62]. Natural remedies have been identified as promising sources for the synthesis and manufacture of antiviral agents [61]. Several antitumor, antifungal, anti-inflammatory, and antiviral metabolites derived from plants and animals have been reported [22]. Herbal plant therapy has long been used for a variety of medicinal uses in Asian countries [61].

6.2. Plants‑Based Treatment

Many reports have focused on natural products obtained from plants as possible antiviral drugs [61,63]. Antiviral properties have been identified for bioactive metabolites extracted from different parts of plant extract, such as stems, seeds, roots, and leaves. The plant *N. sativa* is a good source of thymoquinone. Additionally, the synthesis of hormones, antibodies, and secretion in the treatment of diseases is heavily dependent on human or animal-derived remedies. In the critical stage of COVID-19 therapy, plasma treatment is an example of a particular remedy [61].

6.3. Synthetic Remedies

Allopathic therapy is described as using Western-style methods to treat any disease. Antiviral medications are approved for patients with pneumonia and a positive coronavirus screen, but supplemental oxygen is strongly recommended in emergency situations. Due to the widespread dissemination of COVID-19, previously identified antiviral, antimalarial, or antiparasitic drugs such as riboflavin, lopinavir, oseltamivir, lopinavir/ritonavir, minocycline, tocilizumab, ribavirin, niclosamide, and corticoster. Clinical and experimental studies are difficult for new drugs, which are still being researched. Few medications have shown to have positive results such as ivermectin, remdesivir, and chloroquine [61].

7. Benefits and Risks of Conventional and Synthetic Medications

Natural remedies are advantageous since they have a strong binding affinity, are safe, and have less side effects, while pharmaceutical remedies are highly reactive that can trigger harm to other tissues or organs in the human body indirectly. Although the benefits that natural and synthetic remedies have been documented to have, the efficacy of all remedies is mostly dependent on the patient's situation and the therapeutic protocol chosen. However, as opposed to natural therapies, unnecessary dose of pharmaceutical remedies is quite dangerous. Natural treatments had more benefits and were safer, with less side effects.

8. Natural Ingredients that may be Anti-COVID-19

Even though developing bioactive natural products against a particular disease, such as COVID-19, is easier than developing vaccines, owing to the variety of natural metabolites, their chemical sophistication, and extraction, it is still a difficult job. Digital scanning for bioactive compounds is a valuable method in natural goods analysis since it decreases the amount of time expended on phytochemical screening of several natural products extracts. *In silico* molecular docking is the term for this process [64,65,66]. Natural metabolites from various chemical groups showed positive virtual molecular docking results nearly 45 days after COVID-19 became pandemic [64]. Da Silva Antonio *et al*., 2020 [64] reported that several chemical groups, including flavanones, flavonols, alkaloids, fatty acids, quinones, terpenes, and steroids had comparable binding energy or docking score to repurposed medications such as remdesivir and chloroquine with proteins involved in COVID-19 replication, including ACE2, 3CLpro, and TMPRSS2. Because of the first observation about COVID-19 replication and the role of this enzyme in the development of the danger community, most docking evaluations were based on ACE2 inhibitors [64,67].

8.1. *N. sativa* Black Seed: A Natural Alternative to Chloroquine

The black seed of the annual flowering plant *N. sativa*, which belongs to the Ranunculaceae family, has been used for a variety of medical purposes. Rheumatoid arthritis, asthma, inflammatory diseases, diabetes, and digestive disorders have all been linked to the use of black seeds and their oil [3,68,69]. Unsaturated fatty acids (26 to 38%), proteins, alkaloids, saponins, and essential oil are all found in *N. sativa* seeds (0.4 to 2.5%). In the seed extract, GC/MS analysis indicated a combination of eight fatty acids and 32 volatile terpenes [68]. The primary active ingredients are thymoquinone, dithymoquinone (nigellone), thymohydroquinone, and thymol. The volatile essential oil's main component (28 to 57%) is thymoquinone [68,70]. Nigellicine, nigellidine (indazoles), nigellimine, and nigellimine *N*-oxide (isoquinolines) are the primary alkaloids identified from *N. sativa* seeds. Palmitic, glutamic, ascorbic, and stearic acids; arginine; methionine; lysine; glycine; leucine; and phytosterols are among the other ingredients [71]. A variety of bioactive components, including nigellimine, are structurally comparable to

chloroquine and hydroxychloroquine. Thymoquinone has been given considerable attention among the active medicinally bioactive compounds of *N. sativa* [50]. *N. sativa* oil and thymoquinone, for example, have been demonstrated to have antinociceptive effects by indirectly activating the supraspinal μ1- and κ-opioid receptor subtypes [68,72]. In addition, due to its antagonistic interaction with the endogenous opioid system, brain endogenous angiotensin II has been postulated to be implicated in central nociceptive pathways [73]. Furthermore, hemorphins, which are opioid active peptides, have been demonstrated to block ACE. These findings imply that opioid receptors and ACE inhibitory chemicals are comparable. As a result, thymoquinone might potentially disrupt ACE2. To put it another way, thymoquinone may prevent SARSCoV-2 from infecting pneumocytes through the ACE2 pathway [68]. As a result, both nigellimine and thymoquinone from *N. sativa* might be used to treat COVID-19 patients.

8.1.1. The Plant *N. sativa* and its Phytoconstituents

N. sativa is a tropical and subtropical annual herbaceous plant in the Ranunculaceae family that thrives in loamy soils [1]. The plant grows to a height of 20–60 cm and produces exquisite blooms with many seeds [74]. It has thread-like leaves and produces exquisite blooms with numerous seeds. The plant is a branching, upright herb with a tap root system, split leaves, and lovely blooms that range in color from yellow to white. Except for the stamens, which are many, the plant is pentamerous [1]. *N. sativa* has been routinely and abundantly farmed for numerous uses throughout Asia, Europe, the Middle East, and other Mediterranean nations [75]. The plant is typically grown in the spring and harvested in the autumn; however, this might vary slightly depending on geographic region. *N. sativa* takes around six months to develop from seed to harvest. It is mostly grown for the seeds, which are used as spices, flavorings, and medical cures, particularly in South Asia. Thymoquinone, thymol, α-phellandrene, oleic acid, proteins, and carbohydrates are the most important chemical elements in *N. sativa* [1,3]. The primary components of black seeds have previously been extracted and identified as oleic acid, palmitic acid, linoleic acid, and trans-anethole [1]. Venkatachallam *et al*. [75] discovered that the plant contains phenolics and Quinones in their research (thymoquinone, thymol, dithymoquinone, and thymohydroquinone). Additionally, Harzallah *et al*. [76] identified 48 distinct chemicals from black seed oils, the majority of which were thymoquinone. Benkaci-Ali *et al*. [77] found that *N. sativa* seeds produced a variety of compounds, the majority of which were monoterpene hydrocarbons. Proteins, lipids, phenols, and alkaloids were found in *N. sativa* seeds, according to Piras *et al*. [78]. Srinivasan [23] has reported that the plant contains a variety of biochemicals, primarily phenols, terpenes, and flavonoids.

8.1.2. Uses of *N. sativa* in Herbal Medicine

N. sativa seeds have a variety of therapeutic qualities. The plant has been used to treat asthma, hypertension, gastric diseases, liver diseases, immunological disorders, cancer, neurological disorders, and a variety of other ailments in herbal therapy [1,79]. A summarized Table of various health issues as well as the efficiency of Nigella seeds in treating them can be found in the work of Majdalawieh & Fayyad [79].

8.1.3. Role of *N. sativa* in the Treatment of Asthma

More than 0.3 billion individuals worldwide suffer from asthma, a respiratory illness linked to genetic or environmental causes [1,80]. *N. sativa* seeds, oil, and herbal tea have been used to treat acute and chronic asthma in several parts of the world. According to Boskabady *et al*. [11], boiling extracts of *N. sativa* seeds effectively alleviated asthma-related illnesses in asthmatic patients when given daily for three months. The administration of 1–2 g of *N. sativa* per day to asthmatic patients resulted in a partial improvement in their conditions [81]. When patients were given a 500 mg capsule twice a day, Koshak *et al*. [82] discovered that the seed oil helped to reduce asthma. Ethanolic extracts and oil [1] dramatically decreased histamine release and alleviated asthmatic symptoms in rats in animal studies. When guinea pigs were given *N. sativa* oil instead of a control group, airway inflammation was decreased, and asthma was managed [83]. *N. sativa* appears to contain these qualities that contribute to significant asthma control, since typical anti-asthmatic drugs operate as dilating agents of the airways in addition to their anti-inflammatory actions.

9. Conclusion

The promotion of novel medication development based on extracts from traditional medicinal plants should be supported as the globe frantically hunts for new therapies to minimize COVID-19-related severe morbidity and death rates. *N. sativa* is a popular medicinal plant in the Ranunculaceae family, with a variety of health advantages and proven therapeutic effects for a variety of ailments. Since ancient times, the seeds, in their complete form, as well as their extracted forms and oils, have been utilized to cure a variety of ailments. It contains several active compounds, including thymoquinone, which has been

shown in several studies to have anticancer, anti-diabetic, and hepatoprotective properties.

Antiviral agents from natural and synthetic products have been extensively developed in the quest for new antiviral drug therapies. This research found that medications obtained from natural materials as bioactive antiviral compounds have a higher chance of curing coronavirus infection than generic drugs with less side effects. Scientific trials on the appropriate and successful medicinal use of COVID-19 are also underway, which authentically confirms the patient's chances of survival and the medication's toxicity, as well as the efficacy of drug synthesis in inhibiting viral infection and replication. This review is especially relevant since it discusses new therapies for coronavirus disease using natural products like *N. sativa*. Scientists are searching for more effective future cures for coronavirus illnesses regardless of the advantages and side effects. The research clearly shows that *N. sativa* is beneficial in the treatment of asthma, analgesia, ulcerative colitis, gastroenteritis, wound healing, obesity, hypertension, and cardiovascular disease. Because of its broad therapeutic potential, *N. sativa* should be widely used in both traditional and modern medication systems.

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CONFLICT OF INTEREST
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