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Antiviral potential of black cumin (*Nigella sativa* L.) against viral diseases: A comprehensive review

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Abstract

Nigella sativa L. is a seed spice that is known all over the globe as black cumin, roman coriander, kalonji, kalajeera. It is also highly regarded as herbal therapy, and it is possible to use it as a liquid medicine to boost immunity while reducing the risks associated with acute respiratory distress syndrome. The primary components found in essential oil of *Nigella sativa* are thymoquinone (TQ), dithymoquinone (DTQ), and thymohydroquinone (THQ), which are mainly associated with the antiviral properties. This article highlights the inhibitory effects and potential use of compounds against many viral diseases including Influenza, HIV, Chickungunya, Hepatitis C Virus, hepatitis A viruses and coronavirus. There is still a need for additional research to be conducted in both *in vitro* and *in vivo* order to fully understand the mechanism by which these compounds exert their therapeutic benefits. Further preclinical and clinical tests should be run against COVID-19 in order for researchers to study at the cellular targets, both particular and molecular.

Keywords: Thymoquinone, Coronavirus, HIV, thymohydroquinone, Hepatitis, Influenza

1. Introduction

Globally, there is a great concern due to the terrible threat that viral infection pose to people and there are constant reports of new viral diseases with serious health problems, since there is no efficient antiviral treatment (Kapoor *et al.*, 2017) [28]. There is a growing risk of developing alpha viruses and flavi-viruses to cause viral illnesses such as Influenza, HIV, Chickungunya, and other diseases. Recently, the whole mankind was badly impacted by the pandemic (COVID-19), which was caused by newly identified coronavirus. Due to viruses' ability to change their genetic makeup and acquire medication resistance, it is now more challenging to develop effective treatments and antivirals (Irwin *et al.*, 2016) [25]. Additionally, antiviral medications show negative side effects and these consequences have impact on human health both directly and indirectly. This promotes the creation and discovery of natural plant-based herbal remedies with few negative impacts (Biswas *et al.*, 2020) [7].

Nowadays, programs for research and development are consistently utilizing various seed spices and their products for developing the new pharmaceuticals. Among all the seed spices, *Nigella sativa* L. possess several properties. It is a popular food supplement and therapeutic remedy in various cultures and typically referred to as black cumin, black caraway, kalajeera or roman coriander in various parts of the world (Allah *et al.*, 2021) [75]. The *Nigella sativa* plant has a long history in religion and history as an enchanting culinary remedy (Shrestha *et al.*, 2012; Zaidi *et al.*, 2015; Ijaz *et al.*, 2017; Ikhsan *et al.*, 2018) [56, 69, 23, 28]. It is originated in Southern Europe, North Africa and Southwest Asia (Lal *et al.*, 2020) [71]. They further reported that it is widely grown and consumed throughout India, particularly in Punjab, Bihar, Himachal Pradesh, Madhya Pradesh, Bengal, Assam, Rajasthan and Maharashtra.



Fig 1: Black cumin flower and seeds

2. Phytoconstituents of *Nigella sativa*

Black cumin is referred as miracle herb because it possesses wonderful power of healing and the seeds are effective for treatment of variety of diseases and conditions (Kaushik and Barmanray, 2022) [29]. Indian and Middle Eastern cuisines utilize kalonji seeds as a spice because of their spicy bitter taste and aroma (Hangargekar *et al.*, 2020) [21]. According to Kaushik and Barmanray, (2022), depending on the region, these seeds contain protein (18.67-20.85%), carbohydrates (17.51-30.9%), fibre (5.50-7.33%), fat (45.09-50.0%), alkaloids, tannins, saponins, minerals such as copper (1.79-3.44 µg/ml), Zinc (1.24µg), Potassium (1.94 µg), Magnesium (0.30 µg), Calcium (2.63 µg/ml) along with the presence of vitamin A, ascorbic acid, thiamine, niacin, pyridoxine and folate and thymoquinone, dithymoquinone, thymohydroquinone and thymol are the major bioactive compounds present in kalonji seeds. Terpenes, flavanoids, phytosterols, tannins, coumarins, phenolic compounds, alkaloids, saponins, fatty acids, and volatile oils were found

in *Nigella sativa* during phytochemical screening (Maideen *et al.*, 2020) [40]. Khan and Afzal, (2019) [31] reported on bioactive compounds of black seeds and acclaimed several therapeutic qualities, including anti-diabetic, bronchodilatory, hypotensive, antiviral, antibacterial, antifungal, analgesic, anti-inflammatory, and immunopotentiating, make black seeds a crucial immune enhancer by boosting human immunity. In fact, this seed spice has occupied a special place in COVID-19 pandemic for its important medicinal applications. It is used in preparing a healthy concoction (*Kaddha*) mixing with other spices which has been used as immunity booster to fight against the corona infection (Khazdair *et al.* 2021) [32].

3. Health benefits of Black cumin seeds

Recent Research revealed that volatile oil of black cumin has 67 active components, several of which are capable of producing advantageous health benefits in human body. Several studies have been demonstrated the insecticide, bronchodilator, bacteriological, choleric, antitumor, antiviral, hypotensive and immune-modulative properties. Also, COVID-19 patients with comorbid illnesses could benefit from its properties against hypertension, obesity, diabetes, hyperlipidemia, ulcers, and antineoplastics. Additionally, nigellidine and alpha-hederin, both are the active ingredients of black cumin, which have been discovered as potential SARS CoV-2 inhibitors (Salim and Nouredine, 2020) [51].

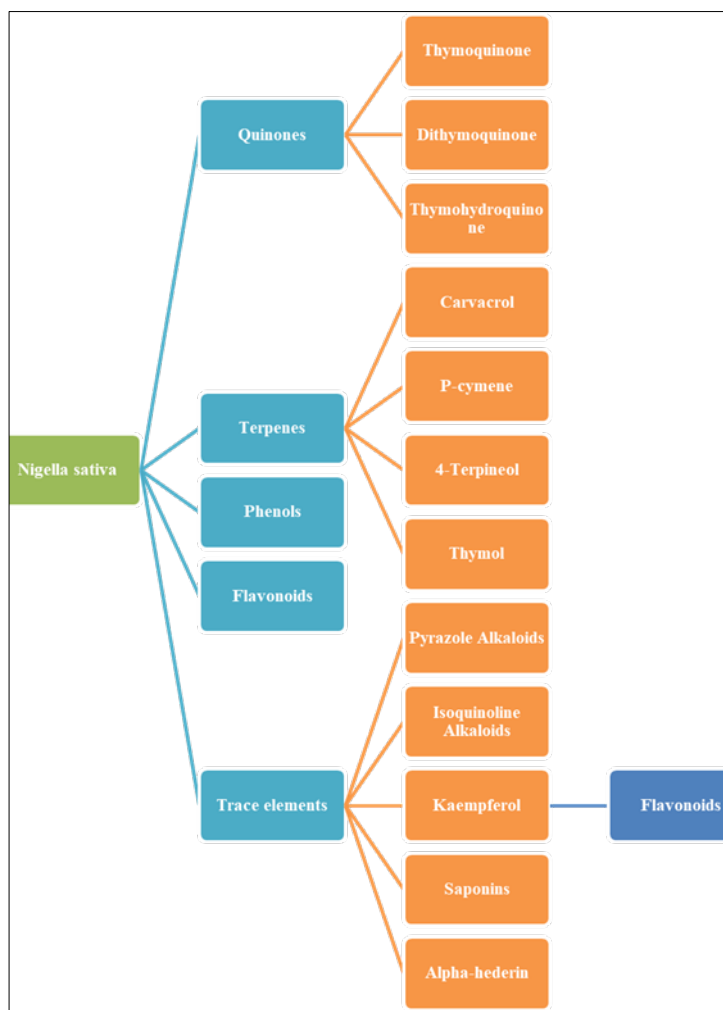


Fig 2: Phytoconstituents of *Nigella sativa* (Kooti *et al.*, 2016; Majeed *et al.*, 2021) [33, 41]

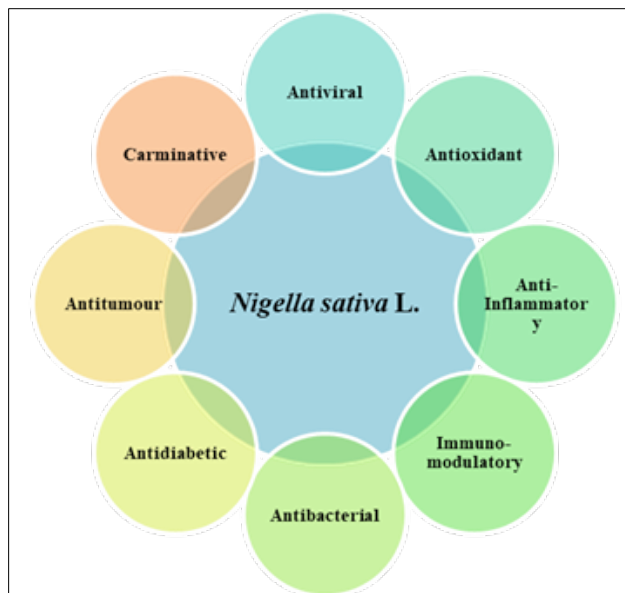


Fig 3: Health beneficial properties of *Nigella sativa*

4. Antiviral Activity of Thymoquinone

Natural substance thymoquinone is one of the primary constituents of black cumin that has shown promise in the development of drugs to combat coronaviruses like SARS-CovV-2. The immune-modulating properties of thymoquinone (Sommer *et al.*, 2020) [59] are well known, and it is likely associated with its antiviral properties. Black cumin contains 30% to 48% TQ (2-methyl-5-isopropyl-1, 4-benzoquinone), a monoterpenoid that has a variety of beneficial bioactivities, and is a monoterpenoid that accounts for 30% to 48% of the volatile oil. It accomplishes this by inhibiting the production of pro-inflammatory cytokines and enhancing the levels of anti-inflammatory cytokines such as IL-4 and IL-10. These two cytokines are responsible for the anti-inflammatory effect (Goyal *et al.*, 2017) [18]. In comparison to TQ, thymohydroquinone (THQ) possesses more potent antioxidant properties and offers superior protection against cell damage (Staniek and Gille, 2010) [60]. A number of clinical experiments have demonstrated that *Nigella sativa* is particularly suitable for treating HIV and HCV infections in people infected with HIV (Maideen *et al.*, 2020) [40].

An intriguing research project involved the administration of *Nigella sativa* oil to mice that had been infected with "Murine cytomegalovirus (MCMV)," which is a DNA-virus with host specificity for mice. On day 3 of infection, the black seed oil displayed a startlingly total reduction of the virus titres in both the spleen and the liver, whereas the MCMV virus was evident in the mice that received no treatment (Salem and Hossain, 2000) [50]. In turkey chicken, nigella seeds dramatically reduced the virulence of the H9N2 influenza virus and increased immune response (Umar *et al.*, 2016) [65]. In a clinical trial, *Nigella sativa* was given to Hepatitis C virus (HCV)-positive Egyptian patients who were not eligible for IFN/ribavirin therapy, including some diabetic and HCV-positive patients. The treatment lasted up to three months (450mg three times daily). After the therapy period, patients generally showed varying degrees of improvement in their clinical conditions, decrease in viral loads, oxidative stress, and glycaemic control in diabetic patients (Barakat *et al.*, 2013) [6]. According to an unexpected case study, an adult with HIV

who was treated with *Nigella sativa* for up to six months (Dose 10ml twice a day) had unexpectedly negative results from a follow-up "EIA Western Bolt" test on day 187 of treatment; this result was confirmed as sero-negative through multiple tests, demonstrating the plant product's efficacy as an anti-HIV agent (Onifade *et al.*, 2013) [48].

5. Preventive effects of *Nigella sativa* against viral diseases

A number of *in vitro* studies have demonstrated the antiviral activity of *Nigella sativa* against a variety of viruses (Molla *et al.*, 2019) [43]. This herbaceous plant has been shown to be virucidal against herpes simplex and hepatitis A viruses (Barakat *et al.*, 2020) [72]. *Nigella sativa* decreased Coronavirus load in HeLa cells by increasing interleukin 8 secretion and downregulating TRPM6, TRPA1, TRPC4, TRPM7, and TRPM6 genes (Koshak and Koshak, 2020) [34]. There is evidence that *Nigella sativa* suppresses the growth of influenza virus (H5N1) *in vitro* (Dorra *et al.*, 2019) [11] as well as the replication of hepatitis C virus (Oyero *et al.*, 2016) [49]. As a result of docking nigelledine with 6LU7 active sites, in terms of the energy complex scores, Favipiravir and hydroxychloroquine were less effective than chloroquine and performed similarly. Compared to chloroquine, hydroxychloroquine, and favipiravir, the energy scores of the saponin α -hederin docked with 2GTB active sites were much greater. (Bouchentouf and Missoum, 2020) [9].

The most important pathophysiological characteristic of COVID-19 patients is lung inflammation, which is induced by the interaction of immunological and oxidative mechanisms (Danzi *et al.*, 2020) [10]. Therefore, the primary objective for the successful treatment of COVID-19 is to identify a medicine that has both protective and multipotential effects and can put an end to such respiratory discomfort. Immune-boosting properties of black seed have been studied by a large number of researchers in the context of respiratory distress. All of the investigations have demonstrated that the pathways of acid arachidonic metabolism that are associated with cyclooxygenase and 5-lipoxygenase were suppressed by the *Nigella sativa* (Goyal *et al.*, 2017) [18]. According to Hossein *et al.*, (2008) [22], the effectiveness of black seeds in lowering lung inflammation provided evidence of the plant's ameliorating action; this may be a result of its ability to inhibit the proliferation of leukocytes and eosinophils in the blood due to its anti-inflammatory and antioxidant properties. Its therapeutic potential is determined by the presence of nigellone and carbonyl polymer of thymoquinone (TQ), which reduce intracellular calcium levels, inhibit protein kinase C, and enhance oxidative energy by inhibiting histamine release from peritoneal mast cells (Kulyar *et al.*, 2021) [36]. Results indicated that some natural compounds found in *Nigella sativa*, including nigellidine, α -hederin, hederagenin, thymohydroquinone, and thymoquinone, might inhibit the Coronavirus. To determine *Nigella sativa*'s ability to inhibit Coronaviruses, preclinical evidence must be obtained. It is suggested that *Nigella sativa* be tested clinically in patients with COVID-19 if preclinical investigations confirm its active effects (Maideen *et al.*, 2020) [40].

5.1 *Nigella sativa* against Herpes viruses

It is well known that *Nigella sativa* and TQ are effective antiviral treatments for herpes viruses. Herpes virus is an

ubiquitous component of the huge family of DNA viruses known as Herpesviridae, with the herpes viruses being the most prevalent subfamily. These viruses are known to spread a wide range of illnesses to both humans and animals. Herpes viruses are categorised as herpes simplex viruses HSV-1, HSV-2, HSV-1 causing mouth ulcers and HSV-2 causing genital ulcers, despite the fact that HSV-1 has been related to genital infections (Van Lint and Knipe, 2019) [67]. According to projections made by the WHO in 2012, 3,709 million people worldwide were infected with HSV-1 (67% of the global population), whereas 417 million people were infected with HSV-2 (11.3 percent of the global population) (Looker *et al.*, 2015) [38].

A study that examined the antiviral activity of *Nigella sativa* against HSV-1 and HSV-2 found that although it was damaging to the host cell, it did have a slight antiviral effect against HSV-1 (with an IC₅₀ value of approximately 50 g/mL vs. HSV-2), (Sokmen, 2001) [58]. Epstein-Barr virus (EBV) is another herpes virus that has been investigated extensively alongside herpes simplex virus (HSV) and herpes cytomegalovirus (MCMV), (Zihlif *et al.*, 2013) [70]. Previous research has shown that *Nigella sativa* has antiviral properties supported the current findings by attributing the TQ, which is the major bioactive ingredient in black cumin, has been shown to have antibacterial activity against a variety of microorganisms, including fungus, bacteria and viruses (Randhawa *et al.*, 2017) [73].

5.2 Effects of *Nigella sativa* against Human Immuno deficiency virus (HIV)

The most widespread public health issue today is still thought to be HIV infection. To this day, the transmission of the HIV is considered to be the most pressing health issue worldwide. According to the WHO's estimate from November 2019 (WHO, 2019) [68], over 32 million people have died from HIV/AIDS since it was first diagnosed in 1981 (UNAIDS, 2006) [66]. According to the most recent estimates (World Health Organization, 2019) [68], there were 37.9 million individuals living with HIV all over the world at the end of 2018.

For its part, HIV is a lentivirus that belongs to the family Retroviridae. It is possible for HIV-infected patients to develop AIDS, in the final stage of HIV infection. HIV weakens immune system by attacking the body's CD4 cells. This makes it difficult for healthy people to recover from common diseases. Depending on the individual, a person can have HIV infection for two to fifteen years before developing to the final stage, which causes AIDS (WHO, 2019) [68]. There is currently no HIV prevention vaccine or 100 percent successful HIV treatment. Onifade and his colleagues have examined the usefulness of a combination of *Nigella sativa* and pure honey extracts in the treatment of some HIV patients. By directly lowering the viral load and/or increasing the CD4 count, they reported a variety of HIV-related activities (Onifade AA, 2014) [44].

5.3 Effects against Hepatitis C Virus

According to WHO, the Hepatitis C virus (HCV) infected roughly 71 million individuals in 2015; as a result, elevated liver enzyme expression is widely considered a hallmark of Hepatitis C, a worldwide public health concern. The cytoplasmic levels of these enzymes typically rise after liver injury, making them the most evident indicators of hepatic injury (Hajarizadeh *et al.*, 2013) [19].

According to mortality and morbidity statistics, Egypt is among the world's wealthiest countries. In 2013, the country's death toll was predicted to be between 10 and 15 percent of its total population (Abdel-Moneim *et al.*, 2013; Barakat *et al.*, 2013) [1, 6]. In both investigations, *Nigella sativa* seed oil was found to dramatically reduce viral load and liver enzyme expression in Egyptian HCV patients. Serum total protein and albumin levels significantly increased after taking *Nigella sativa* extract, indicating a marked improvement in health. These two studies confirmed the results of prior research that have examined the effects of *Nigella sativa* on animals (Al-Gaby, 1998; Tollba, 2003; Shewita and Taha, 2011) [3, 61, 55].

5.4 *Nigella sativa* against Influenza virus

The Orthomyxoviridae family, which includes influenza viruses, is divided into subgroups A, B, and C. Fever, headache, sneezing, muscular pains, sore throats, and joint pains are common symptoms of respiratory tract infections; Flu virus infection has been related to more severe infections including pneumonia (Eccles, 2005; Blumel *et al.*, 2009) [12, 74]. The human fatality rate caused by influenza virus infection is thought to be the greatest of any epidemic. Around 40 to 50 million individuals died in the Spanish flu epidemic of the influenza A virus in 1918 (Trilla, and Daer, 2008) [62].

A virus (AIVs) known as avian influenza is split into subtypes based on distinct combinations of several viral surface proteins, such as hemagglutinin (HA) and neuraminidase (NA). Umar *et al.*, (2016) [65] discovered that nutritional supplementation with *Nigella sativa* seeds, TQ, and their combination reduced the clinical symptoms of H9N2-infected birds. In addition, the research found that supplementing with 3% black seeds reduced clinical symptoms. It also found that as compared to 1% food supplementation, the treated turkeys' immune responses were improved and viral pathogenicity was lowered. This dose-dependent impact was later demonstrated to have a greater *Nigella sativa* supplementation at 6% was associated with a higher antibody titre than at 1% and 3%. (Umar *et al.*, 2016) [65]. According to the results of this investigation, gene expression for cytokines increased in turkeys given *Nigella sativa*, resulting in enhanced antiviral actions and decreased pathogenicity of H9N2 viruses. In second study, the thymoquinone content of *Nigella sativa*, which increased the immune response and decreased viral pathogenicity in treated birds, was found to include antiviral properties and demonstrated to significantly reduce clinical symptoms in turkeys fed this combination of thymoquinone and other herbs (Umar *et al.*, 2016) [65]. Furthermore, black cumin extract has been utilized in the past to treat H5N1 avian influenza viruses. Experimental research indicated that the inhibition is mediated by a rise in innate immunity (Dorra *et al.*, 2019) [11]. *Nigella sativa* oil has shown promise as an adjuvant in H5N1 vaccines, although a different study indicated that it can also display non-specification-infective properties and the ability to produce an immune response that prevents further H5N1 transmission (Mady *et al.*, 2013) [39].

6. Protective role of *Nigella sativa* against COVID-19

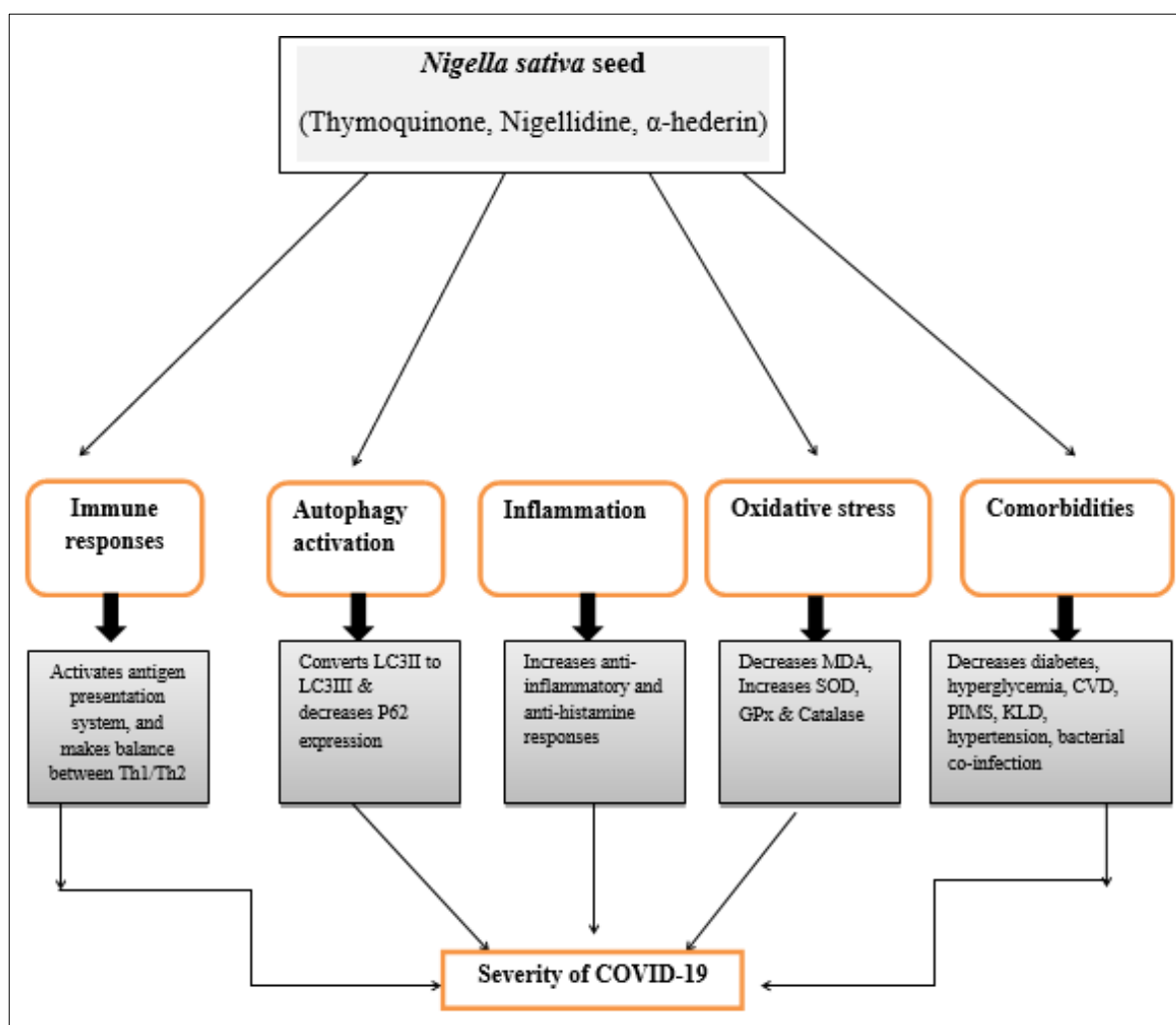
Nigella sativa contains several bioactive compounds that have been related to antiviral, anticancer, and antibacterial effects. These include thymoquinone (27.8%-57.0%), P-

Cymene (7.1%-15.5%), carvacrol (5.8%-11.6%), T-Anethole (0.25%-2.3%), 4-terpineol (2.0%), and longifoline (1.0%). Recent research indicates that *Nigella sativa* extracts can reduce the amount of the SARS-CoV-2 virus by boosting the induction of IL-8 (Ulasli *et al.*, 2014) [63].

The effects of black cumin seed oil on cytomegalovirus infection have been shown to be augmented by CD4+ T cells as well as IFN- γ levels, consequently, cytomegalovirus-infected mice had their viral loads dominated (Forouzanfar *et al.*, 2014) [17]. In diabetic and non-diabetic HCV patients, *Nigella sativa* oil improved the health conditions of patients infected with the hepatitis C virus after administration (Barakat *et al.*, 2013) [6]. Onifade *et al.*, (2013) [48] found that a 46-year-old HIV patient recovered from half a year of treatment with *Nigella sativa*. Following treatment with a blend of *Nigella sativa* and honey, an HIV-positive lady of

middle age recovered from her HIV infection and was able to count her CD4+ T cells. A number of incurable infectious diseases, including HIV, have been suggested to be treated using black cumin seed, but its effectiveness has yet to be determined.

Researchers from the University of Florida found that black seed oil supplementation helped to reduce the viral loads and increased antioxidant activity, total protein and albumin level in patients with hepatitis C virus (Barakat *et al.*, 2013) [6]. Thymoquinone was found to have antiviral properties against avian influenza virus (H9N2) and murine cytomegalovirus (Salem and Hossain, 2000b; Umar *et al.*, 2016) [50, 65]. According to Kuhn *et al.*, (2004) [35], coronavirus spike proteins utilize angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor.



Source: <https://onlinelibrary.wiley.com/doi/full/10.1002/ptr.6895#>

Fig 4: Severity of COVID-19

7. Methods

To find the literature, relating to the antiviral and other properties of *Nigella sativa*, references lists, Google Scholar, Science Direct, Medline/PubMed Central/PubMed, and DOAJ were searched regarding COVID-19 symptoms and indicators utilizing terms like "*Nigella sativa*," "black seeds," and bronchodilatory, immunomodulatory, antiviral, antioxidant, anti-inflammatory, anti-tussive and COVID-19. All research studies examining the antiviral results and additional therapeutic benefits connected to the symptoms and signs of COVID-19 are included in this review.

8. Implications and Limitations

A significant epidemic of COVID-19 poses a grave threat to human health. In extreme situations, host-directed immunotherapies may be a beneficial adjunct to conventional treatment for reducing aggravated pathology and inflammation. An array of immunotherapeutic approaches is available to decrease SARS-CoV-2 outbreaks, reduce viral entry, or target inflammatory mediators (Bonam *et al.*, 2020) [8]. Multiple trials are still continuing and their precise roles in lowering the pathophysiology of COVID-19

remain unknown (Halyabar *et al.*, 2019; Alijotas *et al.*, 2020) [20, 4].

Researchers from all around the world have been working tirelessly to develop a potential cure; unfortunately, there is currently no cure for COVID-19. Although the present method of drug development focuses primarily on reusing existing drugs, it is important to give equal weight to alternative methods, such as pharmacological intervention by natural products. From this vantage point, it's critical to investigate potential alternatives that make use of unconventional resources. Numerous beneficial effects of *Nigella sativa* oil intake and delivery of its active constituents were reported in several COVID-19 comorbidities, including diabetes, cardiovascular disease, and rheumatoid arthritis and a wide variety of bacterial and viral disorders. In this review, we explored the pharmacological characteristics of black cumin seed, a well-known panacea, and its metabolites, including antioxidant, anti-inflammatory, immunomodulation, and induction of autophagy. These characteristics may be essential for interfering with the pathogenesis of COVID-19, which includes immunological dysfunction, oxidative stress, and defective autophagy. Honey and *Nigella sativa* administration in a recent clinical trial against SARS-CoV-2 infection has been initiated with 30 individuals (NCT04347382), (Sohaib Ashraf, 2020) [57]. This experiment may contribute to the development of a novel therapeutic for the management of this pandemic, resulting in a reduction in SARS-Cov-2 infection-related mortality, viral load, and comorbidities. To avoid and monitor COVID-19, it is essential to conduct additional study into the precise mechanisms of action of *Nigella sativa* utilising appropriate preclinical and clinical models.

Thymoquinone's antioxidant, anti-inflammatory, anti-bacterial, and anticonvulsant properties demonstrate a range of therapeutic advantages. Thymoquinone suppresses NF-B activation caused by TNF-, LPS, or other inflammatory stimuli, which significantly reduces the pro-inflammatory response (Sethi *et al.*, 2008) [53]. Studies have shown that thymoquinone can reduce the production of pro-inflammatory cytokines (El Gazzar, 2007) [13] and the expression of inflammatory enzymes such cyclooxygenase-2, 5-lipoxygenase, and leukotriene C4 synthase (Banerjee *et al.*, 2009) [5]. Thymoquinone has a number of positive effects, but it also has several pharmacological limitations that prevent it from being used clinically. These drawbacks include lipophilicity, low bioavailability (Kalam *et al.*, 2017) [27], hydrophobicity (Kazan *et al.*, 2019) [30], heat and light sensitivity (Goyal *et al.*, 2017) [18].

9. Conclusion

This study explored the idea that specific natural compounds could target the molecular pathways of COVID-19 and possibly help people overcome the variety of health issues brought on by the recurrent use of or discontinuation from conventional medications. According to the huge amount of data in the scientific literature, there are numerous studies that black seeds are a generally safe medicament with a long and illustrious history in traditional medicine and possess effective antiviral effects against many viruses. According to scientific studies, seed oil, seed extracts and bioactive components of *Nigella sativa*, especially thymoquinone, have shown promising results in treating various viral infections. As per some recent studies, black cumin or

thymoquinone may be helpful in treating COVID-19, although the precise chemical mechanism by which thymoquinone works against coronaviruses or in COVID-19 patients is yet unknown. However, additional randomised controlled trials are required to confirm the potential benefits of *Nigella sativa* as an alternative herbal treatment for COVID-19 patients.

The majority of the studies that have been published on *Nigella sativa*'s antiviral properties were examined in this review, particularly those that showed the plant's bioactive components to be effective antiviral agents against several human viruses. According to the review's conclusions, additional study is needed to develop *Nigella sativa* as a natural antiviral treatment for a variety of viruses. Hopefully, this summary will serve as a resource for future researchers and inspire more investigation for further research on the antiviral properties of *Nigella sativa* (including *in vitro*, *in vivo*, and clinical trials). In order to find safer medications in the future, additional studies will need to be conducted to investigate the pharmacological interaction and chemical modification of TQ, α -hederin and other components.

Authors Contributions

Nita Kaushik: Conceptualization, Writing Original draft, Review and Editing.

Aradhita Barmanray: Conceptualization, Review, Supervision and Approval.

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy with the approval of the final manuscript for publication.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Declarations

This review article manuscript has not been submitted anywhere else and follows the research ethics.

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