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Thymoquinone: A Promising Natural Compound with Preventive and Curative Properties against COVID-19

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Abstract: *Nigella sativa* seed and its vigorous components, particularly Thymoquinone (TQ), have long been known as a powerful herbal remedy for establishing a balanced inflammatory response, decreasing chronic inflammation, and encouraging a healthy immunological response. *N. sativa* seed essential oil and other formulations offer significant medicinal effects-- antioxidant, immunomodulatory antiviral, antibacterial, and anticoagulant properties. Thymoquinone also boosts the action and number of lymphocytes, cytokine suppressors, natural killer cells, macrophages, and natural killer cells and it has antiviral potential opposition to numerous viruses, along with murine cytomegalovirus, in COVID-19 comorbidities like diabetes, cardiovascular disease, and a variety of bacterial and viral infections. Thymoquinone has proven accurate antagonism to angiotensin-changing enzyme 2 receptors, permitting it to intrude with virus hoisted into the host cell. It might also additionally have an inhibitory impact on SARS CoV2 proteases, which can lessen viral replication. In the context of the COVID-19 pandemic, this evaluation tries to emphasize the capability healing outcomes of TQ.

Keywords: *Nigella sativa*, Black seed, COVID-19, SARS-CoV-2, Thymoquinone, Cytokine storm

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Introduction

COVID-19 is caused by a novel coronavirus that was found in Wuhan, China, in 2019. Since then, it has blowout all across the world, resulting in a global pandemic. SARS-CoV-2 is a transmissible ailment that produces severe acute respiratory syndrome, and COVID-19 is the virus that causes it (Wu *et al.*, 2020). Based on previous outbreak experiences, there is an urgent need to expand public health activities beyond definite clinical management and optimization of provision utilization. Individual and community buoyancy has emerged as the primary provision since the emergence of COVID-19 while remaining the first line of defense in emergency preparedness (Liu *et al.*, 2020). The medical functions of COVID19 range from asymptomatic to acute respiration distress syndrome (ARDS), however, comorbidities consisting of continual ailment and acute organ harm are strongly correlated with ailment severity and mortality in sufferers with COVID19 and multi-organ dysfunction (Zhang *et al.*, 2020).

Nigella sativa is a famous food complement and medicinal plant in one-of-a-kind cultures. The seeds of *Nigella sativa* include numerous effective compounds within the classes of essential oil, saponins, fixed oil, and alkaloids. *Nigella sativa* has traditionally been used as the remedy for diverse sorts of problems inclusive of fever, diabetes, eczema, bronchitis, cough, and influenza (Ali and Blunden, 2003).

In humans, COVID-19 infection causes severe respiratory illnesses and pneumonia-like symptoms (Shanmugaraj *et al.*, 2020). COVID-19 has excessive transmissibility and infectivity as compared to SARS and MERS (Liu *et al.*, 2020). The antiviral, anti-inflammatory and immune-modulatory features of essential oils and natural products are well known (Asif *et al.*, 2020; Kumar *et al.*, 2020). The potential of numerous monoterpenoid phenols produced from plants, containing carvacrol to block viral spike (S) glycoprotein binding to the host cell has been documented (Kulkarni *et al.*, 2020). Carvacrol can also prevent ACE2 activity, which suggests that it may prevent SARS-CoV-2 from entering host cells (Abdelli *et al.*, 2020). This review elucidates the traditional and unique therapeutical characteristics of *N. sativa* and its primary component, thymoquinone, on COVID-19-caused infection inside the respiratory system based on totally anti-inflammatory and antiviral capabilities.

Thymoquinone:

Black seed or *Nigella sativa* (Fig. 1) from the family Ranunculaceae has been established in numerous ancient sites, comprising the tomb of Tutankhamun (Khan, 1999; Ali and Blunden, 2003). Alkaloids and volatile oils are usually related to biological action, and the volatile oils of *Nigella sativa* seeds contain thymoquinone (TQ), thymol, nigellone, dithymoquinone, thymohydro-quinone, α and β-pinene, d-citronellol, p-cymene, d-limonene, 4-terpineol, carvacrol, t-anethole, and longifolene (Fig. 2) (Salem, 2005). Thymoquinone (TQ) (2-Isopropyl-5-methylbenzo-1, 4-quinone) is the chief vigorous constituent of the volatile oil of black seed (Fig. 1d) (El-Mahmoudy *et al.*, 2005). El–Dakhakhny was the first to extract it, and among the numerous active components informed thus far, TQ residues are the most important bioactive principle due to their wide range of therapeutic benefits, including diabetes and cancer. It alleviates the symptoms of asthma, inflammation, arthritis, gastroenteritis, and liver disease. Herbal medicines are made up of bioactive compounds derived from plants (Banerjee *et al.*, 2009). TQ has been linked to variability of pharmacological activities, comprising antioxidant, antihyperglycemic, anti-inflammatory, antihistaminic, immunomodulatory, and anticancer properties. Hepatoprotective, gastroprotective, neuroprotective, and nephro-protective (Fig. 3) (Ma *et al.*, 2015).

Thymoquinone and COVID-19:

Eatable plants and pharmaceuticals have exclusive antiviral properties (Lin *et al.*, 2017). They can directly influence the virus, limit its growth, and increase IFN secretion due to their multi-target and multi-component pattern. *Nigella sativa*, which contains an extensive range of bioactive ingredients such as nigellimine and thymoquinone (TQ), may offer a variety of welfare in the treatment of COVID19, including, blocking virus entry into pneumocytes, offering ionophores to enhance zinc intake, thereby enhancing the host immune reaction to SARS-CoV-2, and stopping virus replication (Ma *et al.*, 2015). COVID-19 and its consequences may be treated well using *N. sativa* seeds and its vigorous ingredients.

TQ had been demonstrated to be useful in lowering cytokine storms and promoting sepsis upshot (Derdeyn *et al.*, 2000). TQ may also have antiviral movement in opposition to avian influenza virus (AIV H9N2) and murine

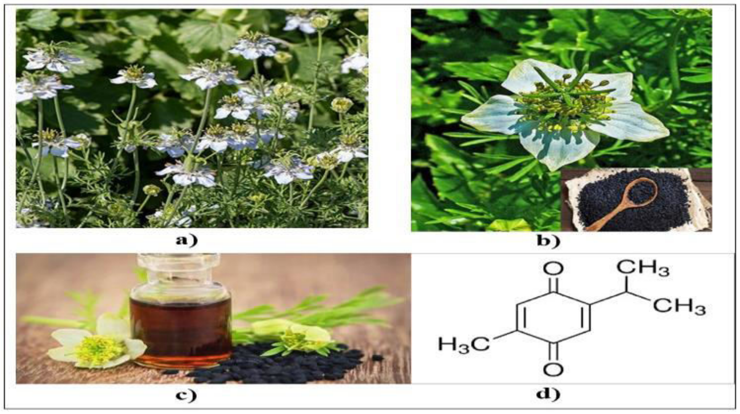

Fig. 1: (a) The *Nigella sativa* plant, (b) Flower and Black seed, (c) Black Seed Oil, and (d) Chemical structure of thymoquinone (TQ).

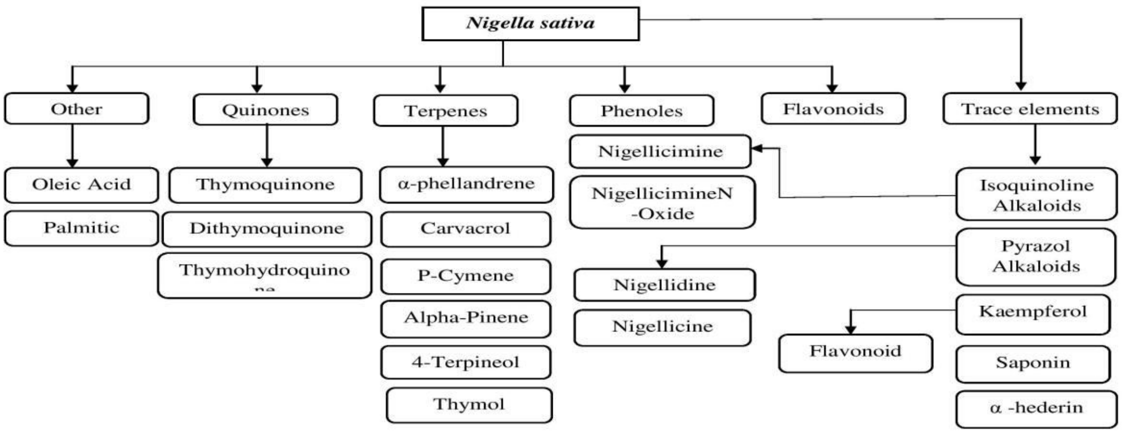

Fig. 2: Biochemical constituents of *Nigella sativa* (El-Tahir and Bakeet, 2006; Ahmad *et al.*, 2013).

Fig. 3: Pharmaceutical values of Thymoquinone (Woo *et al.*, 2012).

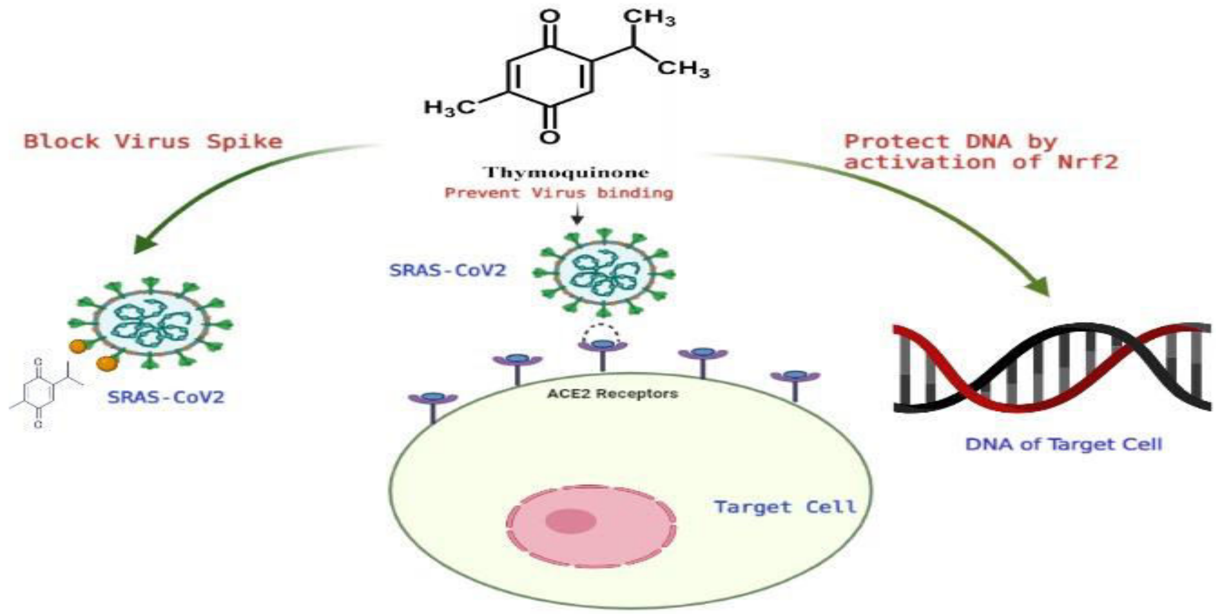

Fig. 4: Action of Thymoquinone at the cellular level.

cytomegalovirus; this antiviral action is achieved by increasing AIV H9N2 antibody titers and lowering coronavirus replication (Hartt *et al.*, 2000). TQ may also impede virus entrance and replication by inhibiting SARS-CoV-2 binding to angiotensin-converting enzyme-2 (ACE-2) receptors (Butt and Sultan, 2010). TQ's powerful anti-oxidant properties can prevent non-enzymatic lipid peroxidation and increase blood flow. TQ ameliorate/reparation endothelial function by inhibiting oxidative stress and restoring the angiotensin system to normal (Tesarova *et al.*, 2011). Decreased NADPH oxidase-dependent superoxide generation and unabated angiotensin networks in cells were also linked to TQ's effects. TQ can also defend the heart from ischemia/reperfusion (I/R) injury, which is linked to anti-oxidative and anti-apoptotic actions through autophagy beginning (Ahmad *et al.*, 2013). Surprisingly, stimulating the Nrf2/HO-1 pathway can effectively reduce myocardial apoptosis and ameliorate coronary microembolization (CME)-induced cardiac dysfunction (Salem, 2005). The advantageous potential of TQ in CVD is believed to derive from its ability to actuate endothelial cells. This increases the creation of NO and endothelial-derived hyperpolarizing factors (EDHF), the formation of the endothelium of vasoconstrictors (such as thromboxane A2), and their effects. Vascular SMC reduces oxidative stress (Jaarin *et al.*, 2015). TQ's activities on the endothelium and SMCs may thereby boost vascular health in COVID-19 sufferers, possibly lowering disease mortality and morbidity (Fig. 4)(Ragheb *et al.*, 2008).

Nrf2 (nuclear factor erythroid-derived 2 related factors 2) is a key transcription factor that protects against oxidative stress by acting as a sensor and precluding genomic impermanence. During a viral infection, intracellular production of viral proteins causes an upsurge in oxidative stress in the cell (El-Gazzar *et al.*, 2007). Nrf2 can now enter the nucleus and motivate the transcription of detoxifying and cytoprotective genes like heme oxygenase (HO-1). Nrf2 has been shown to increase innate immune system activation as well as decrease inflammatory cytokine expressions, such as IL-1, IL-6, and NF-kB, resulting in a reduction in inflammation

(Derdeyn *et al.*, 2000).

COVID-19 rapidity is reversely connected with Nrf2 expression and is directly concerned with age and inflammatory response predominance. TQ functions as a pro-oxidant by activating Nrf2 and boosting its nuclear procurement, which leads to enhanced HO-1 mRNA and protein expression, as well as improved binding to the antioxidant response element (ARE), which lowers ACE2 expression (Banerejee *et al.*, 2009). White blood cells get activated during COVID-19, releasing exceeding, long-lasting inflammatory cytokines, resulting in acute respiratory distress syndrome, numerous organ failures, cytokine storm, and even death. TQ activates Nrf2, which inhibits NF-kB and lowers ACE2 expression, potentially reducing SARS-CoV-2 infection and mitigating the COVID-19-induced cytokine storm and inflammation. This could help cancer patients with high levels of cytokines and inflammation. In cancer patients, however, Nrf2 appears to play a dual role: it defends against chemical and radiation-induced carcinogenesis while also boosting tumor growth (Chehl *et al.*, 2009).

Prophylactic effect of Nigella sativa on SARS CoV-2 infection and co-morbidities:

Hyperglycemia and Diabetes:

Diabetes and uncontrolled glycemia have been linked to increased rapidity and mortality in individuals infected with a variety of viruses, including the 2009 pandemic influenza A (H1N1) (Schoen *et al.*, 2019), SARS-CoV (Yang *et al.*, 2006), and MERS-CoV (Yang *et al.*, 2006; Banik *et al.*, 2016). In 2003, hyperglycemia was discovered in SARS-CoV patients with transitory disruption of pancreatic islet cell activity (Yang *et al.*, 2010). COVID-19 consequences, such as ARDS, pneumonia, and multiorgan failure, are more likely in sufferers with cardiovascular co-morbidity and diabetes. *N. sativa* appears to lower hemoglobin A1c, fasting plasma glucose, and TBARBs while increasing total antioxidant receptivity, containing SOD and glutathione levels (Ahmad *et al.*, 2013). Black cumin seed oil can improve lipid profiles, insulin levels, pancreatic and hepatic antioxidant enzymes, as well as average pancreatic islet extent and glycogen contents (Abdelrazek *et al.*, 2018). Modulating decreasing inflammation (El-Rabey *et al.*, 2017), oxidative status (El-Rabey *et al.*, 2017), serum lipid profiles and monitoring the glucose homeostasis (Daryabeygi-Khotbehsara *et al.*, 2017), growing good cholesterol (HDL-c), with the concurrent exclusion of bad cholesterols (LDL-c, TC, and TG) as well as body mass (Bamosa *et al.*, 2015; Kaur *et al.*, 2018) are very probable features of *N. sativa* as an antidiabetic agent.

The binding affinity of chemicals from *N. sativa* and various antiviral medications with SARS-CoV-2–associated molecular targets such as key main peptidase (2GTB), proteases (6LU7 and 6Y2E), heat shock protein A5 and angiotensin-converting enzyme 2 (ACE2), was determined using molecular docking (Table 1). Nigelledine, an alkaloid found in *Nigella sativa*, had an energy complex score similar to chloroquine and better than hydroxychloroquine and favipiravir when docked with 6LU7 active sites. α- Hederin, a saponin found in *N. sativa*, has a higher energy score than chloroquine, hydroxychloroquine, and favipiravir when docked with 2GTB active sites.

Thymoquinone, the major essential oil ingredient of *N. sativa*, demonstrated lower affinity for binding to the active sites of ACE2, heat shock protein A5 and 6LU7 than hydroxychloroquine in 6LU7 and ACE2. Hederagenin, a saponin found in *N. sativa*, has a lower binding score than saquinavir when docked with the active sites of ACE2, 6LU7, GRP78 and 6Y2E. Thymohydroquinone had modest docking energy with ADP-ribose-1′′phosphatase, SARS-CoV-2 6LU7, endoribonuclease, RNA-dependent RNA polymerase, the binding domain of the SARS-CoV-2 spike protein, and human ACE2. Nigellidine had exhibited highest binding affinity with SARS-CoV-2 enzymes and proteins with significant binding affinity included nonstructural protein 2, N-terminus-proteinase, spike-glycoprotein, 6LU7 and nucleocapsid.

As a result, natural composites identified in *N.*

Table 1: A precis of outcomes ofNigella sativa compounds on severe acute respiratory syndrome-coronavirus disease 2 (SARS-CoV-2) targets (Koshak and Koshak, 2020)

***Nigella sativa* material**	**SARS-CoV-2 targets**	**Control**	**Effects**	**Reference**
Nigellidine	QHD43415_3,6LU7,IL1R,NSP2, QHD43423, TNFR1, 6vsb, TNFR2	NA	Numerous SARS-CoV-2 and inflammatory molecular targets demonstrated an increased affinity for Nigellidine's binding.	(Dorra *et al.*, 2019)
Thymoquinone	6LU7	NA	Thymoquinone's affinity for 6LU7 was acceptable.	(Barakat *et al.*, 2010)
Hederagenin	6Y2E, 6LU7	Saquinavir	Hederagenin had a high affinity for 6LU7, but it was significantly less strong than saquinavir, and 6Y2E was close to saquinavir.	(Oyero *et al.*, 2016)
Thymoquinone	ACE2, 6LU7	HCQ	Thymoquinone demonstrated a substantially lower affinity for binding to ACE2 1R42 and 6LU7 than HCQ.	(Onifade *et al.*, 2013)
α-Hederin, Nigellidine		HCQ	The drug Nigelledine outperformed HCQ and favipiravir.	(Abdelmeguid *et al.*, 2010); (Elgohary *et al.*, 2021)
	2GTB, 6LU7	Chloroquine	With 2GTB and 6LU7, α -hederin and Nigellidine demonstrated a strong binding affinity.	(Ulasli *et al.*, 2014)
		Favipiravir	α-Hederin is superior to HCQ, favipiravir, and chloroquine.	(Barakat *et al.*, 2013)
Thymohydro-quinone	ADRP,6LU7,ACE2, Nsp15/ NendoU,rS,RdRp	NA	Several SARS-CoV-2 molecular targets demonstrated an acceptable binding affinity for thymohydroquinone.	(Romano and Tatonetti, 2019); (Koshak and Koshak, 2020)
Hederagenin	GRP78, ACE2	NA	With ACE2 and GRP78, hederagenin had the highest binding affinity.	(Ahmad *et al.*, 2021)
Thymoquinone	HSPA5	NA	Thymoquinone demonstrated a long-lasting affinity for binding to HSPA5.	(Onifade *et al.*, 2013)

QHD43415_3 = N- terminus-protenase; 6LU7 = main protease; IL1R = interleukin 1 receptor; NSP2 = nonstructural protein 2; QHD43423 = nucleocapsid; TNFR1 = tumor necrosis factor receptor 1; 6vsb = spike glycoprotein; TNFR2 = tumor necrosis factor receptor 2; NA = not available; HCQ = hydroxychloroquine; ACE2 = angiotensin converting enzyme 2; 2GTB = main peptidase; ADRP = ADP-ribose-1″- -phosphatase; Nsp15/ NendoU = endoribonucleoase; rS = binding domain of SARS-CoV-2 spike protein; RdRp = RNA-dependent RNA polymerase; HSPA5 = heat shock protein A5

sativa, such as hederagenin, -hederin, thymohydroquinone, nigellidine, and thymoquinone, were revealed to be possibly efficacious inhibitors of coronavirus. To establish the activity of *N. sativa* in opposition to coronavirus, preclinical data is required. If preclinical studies show that *N. sativa* has clinical activity, a clinical Phase I trial in sufferers with COVID-19 is recommended for further investigation.

Conclusion

This review article summarizes the potential upshots of *N. sativa* and its main component on COVID-19, as well as the underlying mechanism(s) of action. While the entire world hoping for a viable medicine or vaccine to battle COVID-19, researchers had tried to draw interest to the pharmacological potentials of black seed and its bioactive compounds to stimulate additional scientific interest and the adoption of a different strategic approach. Black seed and most of its bioactive compounds have a long history of enhancing immune systems and are easily approachable to people of all socioeconomic backgrounds, as well as providing self-awareness and protection in opposition to COVID-19. This review can provide some useful information for the legitimate public domain, including the fact that *N. sativa* seed and oil can be used as a first-aid kit for COVID-19 prevention; and secondly, to control the deadliest pandemic, bioactive substances like thymoquinone, nigellidine or α-hederin could be studied preclinically and therapeutically for therapeutic improvement, efficiency, and potency under a specific pathophysiological situation.

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