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REVIEW ARTICLE

The role of thymoquinone, a major constituent of *Nigella sativa*, in the treatment of inflammatory and infectious diseases

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Abstract

Nigella sativa (*N. sativa*) is an annual flowering plant that has been used as a traditional remedy for many centuries. The seed possesses a large variety of compounds with thymoquinone (TQ) considered its major but not sole bioactive constituent. Supercritical fluid extraction, geographical location, and oxidative status of *N. sativa* produces the highest yield of essential oil content including TQ. Thymoquinone is lipophilic, heat and light sensitive with low oral bioavailability and rapid elimination that have significantly inhibited its pharmacological development. Novel developments in nanoparticulate-based oral administration, nasal spray and transdermal delivery may allow the clinical development of *N. sativa* and TQ as therapeutic agents. Animal and human studies indicate a potential role of *N. sativa* seed oil and TQ for a diverse range of disease processes including hypertension, dyslipidaemia, type 2 diabetes mellitus, arthritis, asthma, bacterial and viral infections, neurological and dermatological disorders, as it belongs to the group of pan-assay interference compounds. This review outlines the pharmacological properties of *N. sativa* and TQ and their potential wide application for a large variety of human diseases. The paper will focus on recent studies of the anti-inflammatory and antiviral properties that make *N. sativa* and TQ promising therapeutic agents targeting contemporary inflammatory and infectious diseases including Covid 19.

KEYWORDS
Covid 19, oxidative stress, pan-assay interference compound, SARS-CoV-2, supercritical fluid extraction, thymoquinone

1 | INTRODUCTION

Nigella sativa (*N. sativa* or black cumin) is an annual flowering plant belonging to the Ranunculaceae (buttercup) family.[1-3] The plant is native to the eastern Mediterranean, Northern Africa, the Indian subcontinent, and Western Asia.[1,3] The plant grows 20–30 cm long, with a flower containing 5–10 petals and a fruit comprising a capsule of 3–7 follicles that contain black-coloured seeds.[1] These seeds have been used for many centuries as a condiment, food preservative and traditional herbal remedy for multiple diseases including fever, rheumatism, cough, bronchitis, and influenza.[1] *N. sativa* has been referenced in the Old Testament's Book of Isaiah[4] and by the Prophet Muhammad who stated that the black seed is a cure for every disease except death.[5]

Nigella sativa seed possesses a large variety of ingredients including fixed oil, essential or volatile oil, proteins, alkaloids and saponins.[1] Oil content of the seed ranges from 30–40%, of which >98% is fixed and 0.1–2% is essential oil.[3,6] The major oil components include species of triacylglycerol, saturated and unsaturated fatty acids which may vary according to the extraction method used and the seed's origin.[3] Lesser components include phytosterols, tocopherols and essential oils. The essential oil constituents include p-cymene, thymol, thymoquinone (TQ) ($C_{10}H_{12}O_2$ or 2-isopropyl-5-methylbe

nzo-1,4-quinone), dithymoquinone (DTQ) and thymohydroquinone (THQ).[1,3] TQ is the most abundant (30–50%) bioactive constituent of the seed's essential oils and is thought to provide most of its pharmacological effects.[1,2]

Natural products, such as TQ (Figure 1), have distinct structural features including p2 carbon and oxygen atoms rather than nitrogen and halogen atoms, higher numbers of H-bond acceptors and donors and greater molecular rigidity when compared to synthetic molecules.[7] These differences allow TQ and other natural products the ability to interact with proteins and regulate biological processes that confer potential benefit for multiple clinical diseases ranging from cardiovascular disorders to cancer, infectious and inflammatory disorders.[7-10] This review outlines the potential wide application of *N. sativa* and TQ (both hydrophobic and hydrophilic forms) with a focus on recent studies evaluating anti-inflammatory and antiviral properties that make *N. sativa* and TQ promising therapeutic agents targeting contemporary inflammatory and infectious diseases, in particular Covid 19. The review has been subdivided into sections detailing techniques of *N. sativa* extraction, physicochemical and pharmacological properties, anti-inflammatory and antimicrobial properties and therapeutic uses in human subjects.

2 | TECHNIQUES OF *N. sativa* EXTRACTION OF TQ

Nigella sativa seed oil extraction can be achieved using three methods: (i) solvent, (ii) cold press, and (iii) supercritical fluid extraction (SFE). The concentration of TQ and other pharmacologically active components extracted from *N. sativa* seeds demonstrates geographic variation, for example, Iranian derived essential oil has 13.7% TQ concentration as compared to 50% in Indian derived *N. sativa* essential oil.[4] The TQ content in the *N. sativa* extract from the Marche region cultivar in Italy is higher compared with other *N. sativa* extracts produced in the Middle East and in other Mediterranean regions.[11] Thymoquinone and other ingredient content is also influenced by the method of extraction. Solvent extraction may produce detectable traces of organic solvent within the oil as well as cause oxidation and degradation of desired components.[8,9] Cold press extraction has a significantly lower (10–12%) yield of oil content as compared to SFE which can produce 4–5 times higher concentrations of pharmacologically active components, in particular, TQ.[12] SFE also has advantages of being relatively cheap with low toxicity and a good safety profile through use of carbon dioxide as well as low critical temperature and pressure requirements.[13,14] The non-specificity of TQ extracted by SFE may be reduced by combining it with the other fractions present in the extract and/or making it hydrophilic by reducing TQ to THQ.[14]

Nigella sativa seed oil is liquid at room temperature due to its unsaturated fatty acid content with a melting point of −1 to −3°C and differences in colour values (golden to brownish yellow), depending on the method of extraction used. In contrast to crude *N. sativa* seed oil, TQ has a higher melting point of 44–45°C.[15,16]

3 | THE PHYSICOCHEMICAL AND PHARMACOKINETIC PROPERTIES OF TQ

Thymoquinone is a quinone-based phytochemical that was identified in 1963.[16] It is lipophilic and demonstrates sensitivity to heat

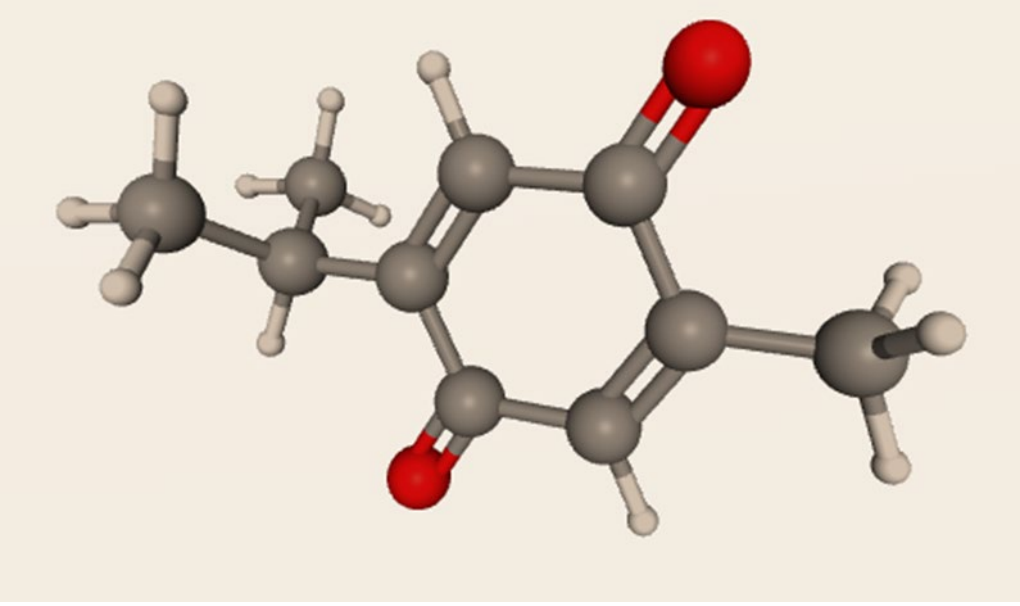

FIGURE 1 Thymoquinone is a p-benzoquinone, where the two C=O groups (grey and red double bond) are attached at the 1- and 4-positions, respectively. It has been classified as a pan-assay interference compound, which can bind indiscriminately to many proteins. Thymoquinone is an extremely weak basic (essentially neutral) compound with a chemical formula $C_{10}H_{12}O_2$. Thymoquinone can target and modulate inflammatory modulators including interleukins and tumour necrosis factor-α

and light.[2] These physicochemical properties limit its bioavailability and have inhibited its pharmaceutical development into a tablet or capsule formulation[2] although TQ can be used as a nasal spray[17] and in liquid, oral bolus and transdermal forms.[18]

Thymoquinone has a low molecular weight of 164.204 g/mol and thus can penetrate the blood brain barrier which is attractive from a neurological drug development perspective due to the anti-oxidant, immunomodulatory and antiviral activity identified in animal models.[15] Its anti-inflammatory, anti-cancer and anti-microbial properties indicate a potential role as a treatment that can target multiple organ system disorders[3,4,13] could be due to the fact that TQ belongs to the pan-assay interference compound group[19,20] and can interact and bind non-specifically with multiple proteins and receptors in the same way as curcumin.[21]

Thymoquinone demonstrates rapid concentration-time elimination properties following intravenous administration.[15] In a pharmacokinetic animal (rabbit) model, TQ had an elimination half-life of 63 ± 11 and 275 ± 8.5 min, following intravenous and oral administration, respectively. It demonstrates rapid elimination and slower absorption following oral administration.[22] TQ is 99% bound to plasma proteins including albumin and alpha-1 acid glycoprotein.[2,15] There is evidence of hepatic biotransformation including reduction of TQ into dihydrothymoquinone as well as interaction with cytochrome P450 enzymes 3A2 and 2C11 that may result in interaction with drugs such as glibenclamide and cyclosporine.[23]

Although there have only been limited studies evaluating toxicity, animal studies indicate a good safety margin between efficacy and potential toxicity following acute and chronic oral and intraperitoneal administration of *N. sativa* seed oil and TQ.[4] Therapeutic doses of TQ in animal studies range from 1–5 mg/kg (intraperitoneal or intravenous) to 20 mg/kg (oral).[24] Long term oral administration of 10 mg/kg body weight to mice has been demonstrated to be safe and well tolerated.[15]

The challenges of its storage, formulation and pharmacokinetic properties have been responsible for its limited pharmaceutical development. However, its multifunctional activity, including potential for broad neurological benefits, warrant investigation of new modes of delivery including utilisation of nanotechnologies. Solid lipid nanoparticles of TQ have been demonstrated to improve bioavailability in animal models with evidence also of selective accumulation in the brain when compared to other organs.[25] Thymoquinone–loaded nanostructured lipid carriers may also have less toxicity than pure TQ.[15] Nano-particulate-based drug delivery systems of TQ may maintain stability, improve bioavailability, and offer a novel future direction for oral formulation and administration. For example, chitosan-coated Poly (lactic-co-glycolic acid) nanoparticles loaded with TQ have been administered intranasally in rats with evidence of enhanced antioxidant activity in the brain consistent with nose-to-brain transport.[26] Transdermal application is another potential modified form of TQ drug delivery worth exploring in the future.[16] Ethanol and propylene glycol as a donor system in conjunction with permeation enhancers has shown promise as a transdermal sustained release formulation of TQ.[27]

4 | PHARMACOLOGICAL ACTIVITY OF *N. sativa* AND TQ

Studies suggest that not only TQ, but several other components of *N. sativa* contribute to its pharmacological effects[14] and the key for securing the seed oil's maximal biological activity, lies in designing the SFE method and in blending the accurate concentration of its fraction.[28] The pharmacological properties of *N. sativa* oil and TQ are reported to be diverse ranging from anti-inflammatory, analgesic, antioxidant, anti-apoptotic, immunological, anti-tumour, neuromodulatory and/or neurocognitive, anti-metabolic including hypolipidemic and anti-hyperglycaemic as well as antimicrobial.[11,29] The following subsection will focus on the anti-inflammatory, immunological and antimicrobial properties of *N. sativa* extracted oil and TQ including its potential therapeutic role against severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] (Covid 19) infection.

4.1 | Anti-inflammatory properties

The mode of action of *N. sativa* extracted oil and TQ is mediated via several mechanisms which include antioxidant, immunomodulating, cytoprotective and inhibitory effects on inflammatory mediators (Table 1).[25] Activation of lymphocytes, macrophages, mast cells, neutrophils and eosinophils in response to antigen exposure and/or host cell injury underpins the inflammatory response associated with auto-immune and infectious diseases. Augmentation of T-cell and natural killer cell-mediated immune responses, modulation of CD4(+)/CD8(+) lymphocyte ratios and enhancement of the oxidant scavenger system are integral to controlling an inflammatory response.[2,4,10] Modulation of the production of interleukins by human lymphocytes and macrophages and/or inhibition of oxidants released during the inflammatory process has been demonstrated with *N. sativa* and TQ.[2,4,10] *In vivo* and *in vitro* studies demonstrate that *N. sativa* has anti-inflammatory effects that may be beneficial in a variety of chronic diseases including cardiovascular diseases, diabetes mellitus, solid cancers, and haematological malignancies.[10,30] Many of the beneficial properties of *N. sativa* extracted oil and TQ are attributable to radical scavenging activity and inhibition and/or interaction with molecular targets involved in inflammation, including pro-inflammatory enzymes and cytokines[24] such as interleukin (IL)-1α, IL-1β, IL-6, IL-10 and IL-18[31] which have also been shown to be differently modulated by fresh and stored extracts from *N. sativa*.[11]

N. sativa oil extract has also been shown to reduce the expression of pro-inflammatory cytokines cyclooxygenase-2 (COX2), inducible nitric oxide synthetase, tumour necrosis factor-α (TNF-α), prostaglandin (PG)-E2 and lipoxygenase released by activated inflammatory and/or damaged host cells within an inflamed joint and hence could be useful in the treatment of osteoarthritis and rheumatoid arthritis.[10,32] TQ at doses of 2.5–5 mg/kg/day has been shown to produce clinical and radiological suppression of arthritis-induced rat models.[33]

TABLE 1 The anti-inflammatory, antiviral and antibacterial properties of *Nigella sativa* and its constituents

	Nigella sativa constituents	Mode of action	Disease states
Anti-inflammatory	*Nigella sativa* extract TQ	IL–11α, IL–1β, IL–6 and IL–18; ↓ COX2, inducible NOS, TNF-α, PG-E2, lipoxygenase	Rheumatoid arthritis; Osteoarthritis[11,31,32]
	TQ	↓ IL–6, IL–12, (CCL)12/MCP–5, CCL2/MCP–1, GCSF ↓ TNF-α and nitrate	Neurodegenerative disorders[36] EAE; multiple sclerosis[12]
	Nigella sativa extract TQ	↓ PG ↓ mast cell histamine release ↓ IgE	Asthma; allergic airway disease[2,42,59]
Anti-viral	*Nigella sativa* extract TQ Nigellidine α-Hederin	↑IL–8, ↓ TRP gene expression ↓ ACE2 receptor ↓HSP A5 binding	Coronavirus[35] including SARS-CoV–2[31,49,68]
Anti-bacterial	*Nigella sativa* extract TQ	Gram positive and Gram negative bacteria ↓ NO and reactive oxygen species	Septicaemia[22,44]

Abbreviations: ACE, angiotensin converting enzyme; CCL, chemokine (C-C motif) ligand; COX2, cyclooxygenase-2; EAE, experimental autoimmune encephalomyelitis; GCSF, granulocyte colony stimulating factor; HSP, heat shock protein; IL, interleukin; MCP, monocyte chemotactic protein; NOS, nitric oxide synthetase; PG, prostaglandin; TNF, tumour necrosis factor; TQ, thymoquinone; TRP, transient receptor potential.

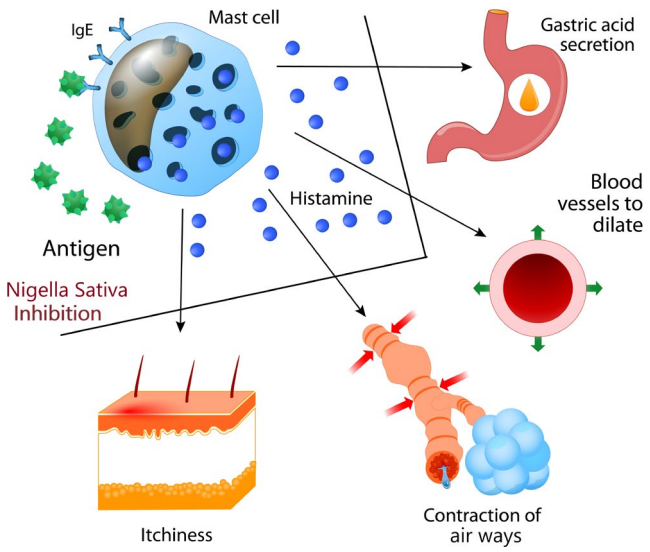

FIGURE 2 *Nigella sativa* has potential therapeutic action for a diverse range of disease processes including respiratory and dermatological though inhibition of histamine release by mast cells

It has also observed that whole *N. sativa* and its purified proteins may suppress as well as stimulate the production of IL-8 in non-activated and pokeweed mitogen-activated peripheral blood mononuclear cells, respectively.[34] Stimulation of IL-8 secretion, inhibition of transient receptor potential gene expression and a reduction in viral load has also been shown in coronavirus infected HeLa cells treated with *N. sativa* extract.[35]

Thymoquinone has been reported to inhibit the formation of the pro-inflammatory cytokines/chemokines in lipopolysaccharide (LPS)-stimulated BV-2 murine microglia cells including IL-6, IL-12p40/70, chemokine (C-C motif) ligand (CCL)12/monocyte chemotactic protein (MCP)-5, CCL2/MCP-1, and granulocyte colony stimulating factor.[36] In relation to the animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), TQ has also been shown to be effective in its treatment[12,37] with evidence of amelioration of inflammation and remyelination of EAE-induced rats even after clinical signs are first seen.[12] Inflammatory markers including C-reactive protein, TNF-α and nitrate have been found to be significantly reduced in EAE-induced adult female rats treated with a hydroalcoholic extract of *N. sativa*.[22,38,39] The anti-inflammatory properties of *N. sativa* may also be responsible for the protective effects seen after trauma-induced neuronal injury[40] and experimentally induced diabetic neuropathy.[41]

The anti-inflammatory benefits of *N. sativa* extracted oil and TQ may include asthma and allergic airway anti-inflammatory benefits through reduced PG production,[2] inhibition of histamine release from the mast cells[42] (Figure 2). Cyclo-oxygenase-2 inhibition by TQ may result in anti-cancer benefits for a wide range of cancers including lung, gastric, breast and pancreatic cancer.[43]

4.2 | Antimicrobial properties

Studies have reported diverse antimicrobial properties of *N. sativa* and TQ including antibacterial, antifungal, antiparasitic and antiviral (Table 1).[1,2] *In vitro* and *in vivo* studies have demonstrated dose-dependent inhibition of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* and *Escherichia coli*.[44] Synergistic antibacterial activity of *N. sativa* extract with several antibiotics ranging from gentamicin, ampicillin, doxycycline, and sulfamethoxazole/trimethoprim combination have been described.[1,45] The modulation of nitric oxide and reactive oxygen species production by TQ may protect against multi-organ dysfunction in the setting of septicaemia.[46]

4.2.1 | SARS-CoV-2 (Covid 19)

The emergence of the global SARS-CoV-2 (Covid 19) pandemic has resulted in an urgent need to find effective antiviral therapies or vaccines. The antiviral actions of *N. sativa* oil include inhibition of murine cytomegalovirus,[1] influenza viruses[2] and Covid 19[46] making the oil's active constituents the subject of contemporary research interest. Thymoquinone, in particular, holds promise as a treatment of SAR-CoV-2 infection as it may inhibit viral proliferation and secondary bacterial pneumonia.[47] Viral replication can be inhibited by several mechanisms including an increase in intracellular pH by the reduced form of TQ.[47] It may also act as an anti-inflammatory and immunomodulatory agent, potentially synergistically with other bioactive constituents of *N. sativa*.[47]

Compounds derived from *N. sativa* oil, in particular TQ, may be effective in inhibiting the ability of SARS-CoV-2 to attach to host cell receptors and replicate within the cell (Figure 3).[46] The mode of entry is through the receptor-binding domain of the SARS-CoV-2 spike glycoprotein attaching to a host pneumocyte angiotensin converting enzyme 2 (ACE2) receptor. Animal and in silico molecular studies suggest that constituents of *N. sativa* including DTQ, the alkaloid nigellidine and α-Hederin, a water-soluble saponin found in *N. sativa*, possess moderate affinity with SARS-CoV-2 enzymes and proteins.[22,46,48] Molecular docking studies indicate that TQ can inhibit the binding of SARS-CoV-2 with ACE2 receptors and cell-surface heat shock protein A5 (HSPA5) which are host-cell receptors recognizable by the SARS-CoV-2 spike protein.[36,49] ACE2 is widely expressed in human respiratory epithelial cells and is important in endocystosis of the SARS-CoV-2 virus into the respiratory cell cytoplasm where the virus is then activated by transmembrane protease serine 2 (TMPRSS2) for protein priming, replication and release to infect other cells and spread the viral infection.[31] Blockade of the attachment of SARS-CoV-2 to HSPA5, which is upregulated in stressed cells, may also reduce the risk of infection.[46] A recent surface plasmon resonance study has also found that TQ can inhibit not only SARS-CoV-2 but also SARS-CoV and human CoV-(NetherLand) NL63 pseudoparticles from infecting Human Embryonic Kidney (HEK)293-ACE2 cells.[50] *Nigella sativa* components including TQ and nigellimine may also potentially act synergistically with other immunomodulatory and antiviral therapies currently trialled in SARS-CoV-2 (Covid 19) infection such as zinc.[51] Hence, TQ and other *N. sativa* compounds, alone or in combination, may be effective treatment in patients with Covid 19.

Covid 19 is also associated with an aggressive inflammatory and hyperactive host immune response to the SARS-C0V-2 virus which is commonly referred to as a 'cytokine storm'.[52] Proinflammatory cytokines/chemokines, including multiple interleukins and TNF-α, are elevated in Covid19 patients and contribute to worse patient outcomes.[52] *Nigella sativa* and TQ may be potentially beneficial in downregulating this inflammatory process and thereby reducing the severity of acute respiratory distress syndrome.[51,52] *Nigella sativa* and TQ also possess anticoagulant properties that may offer both as potential therapeutic natural products targeting the coagulopathy associated with life-threatening SARS-CoV-2 (Covid 19) infection.[53]

4.2.2 | Other viruses

Nigella sativa possesses in vitro antiviral activity against herpes simplex, hepatitis A and C viruses.[1,2,53] There is also evidence that *N. sativa* honey may inhibit the replication of Human Immunodeficiency Virus (HIV)-1.[53]

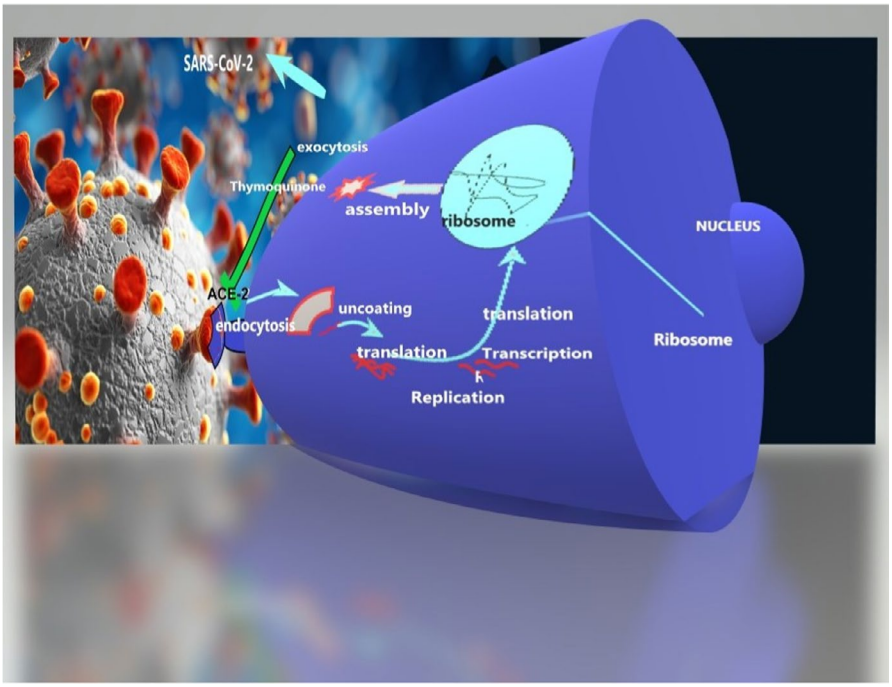

FIGURE 3 Thymoquinone may prevent SARS-CoV-2 virus receptor interaction by inhibition of the attachment of the viral spike glycoprotein to the Angiotensin Converting Enzyme 2 (ACE2) receptor and the priming of SARS-CoV-2 virus through TMPRSS2 (transmembrane protease serine 2)

5 | THERAPEUTIC USES OF *N. sativa* OIL AND TQ IN HUMAN SUBJECTS

5.1 | Clinical studies

There have been numerous published preclinical and clinical studies of the use of *N. sativa* and its constituents in human subjects. Clinical studies have been limited to case series or randomised trials usually involving *N. sativa extract* as opposed to TQ and fewer than 100 patients. The majority of randomised controlled trials have evaluated the potential benefits of *N. sativa* in the treatment of hypertension, dyslipidaemia and diabetes mellitus.[10,54-57] However, there are a limited number of studies which have evaluated the effects of *N sativa* on a variety of conditions ranging from viral illnesses to inflammatory respiratory diseases such as asthma, allergic rhinitis and chronic mucosinusitis, rheumatoid arthritis and osteoarthritis, neurological and dermatological disorders.[10]

5.2 | Antiviral including SARS-CoV-2

There has also been research suggesting a therapeutic effect of *N. sativa* as an antiviral agent in human including potential for its use in SARS-CoV-2[45,46] as supported by molecular docking studies previously outlined.[44] Clinical trials in western Asia have been registered during 2020 which aim to assess the role of *N. sativa* seed oil as adjuvant therapy in hospitalised patients with SARS-CoV-2 (Covid 19) [NCT04347382, NCT04401202]. There are also case reports and small case series exploring the role of *N. sativa* oil as a potential pharmacotherapeutic agent in human subjects with hepatitis C and HIV infection.[53]

5.3 | Asthma and sinusitis

The effect of boiled extract effect of *N. sativa* on 15 asthma sufferers using doses of 50–100 mg/kg was compared to theophylline and found to significantly improve measures of pulmonary function including forced expiratory volume and peak flow although less so than theophylline.[58] In another study of 76 asthma patients, in which maintenance inhaled therapy was supplemented with 1 and 2 g/day *N. sativa* versus control, those treated with *N. sativa* were found to have significant improvements in forced expiratory volume and peak expiratory flow as well as a reduction in serum 1gE levels.[59] *N. sativa* oil and nasal spray have also been reported to reduce IgE levels and nasal mucous congestion in patients with allergic rhinitis[60] and sinonasal outcomes in patients with chronic mucosinusitis,[17] respectively.

5.4 | Rheumatological disorders

Nigella sativa oil has been studied in randomised controlled trials as a capsule and topical oil in the treatment of rheumatoid and osteoarthritis, respectively.[61,62] Differences in serum malondialdehyde and nitrous oxide were found in a study involving 42 female patients with rheumatoid arthritis but there were no differences seen in other factors including IL-10 and TNF-α or in disease activity scores.[61] In contrast, a study involving 52 older patients with osteoarthritis found that topical *N. sativa* oil achieved more effective pain relief compared to diclofenac gel.[62]

5.5 | Neurological disorders

Thymoquinone has antioxidant and antiapoptotic properties through reduction in glutamate-mediated neurotoxicity making it and *N sativa* seed oil attractive as neuromodulatory agents (Figure 4).[29] Hence, TQ and *N sativa* may have a therapeutic role in the neurodegenerative diseases and epilepsies. *Nigella sativa* has been reported to improve executive function, mood, and anxiety in elderly human subjects.[63] Thymoquinone at a dose of 1 mg/kg and *N. sativa* extract 40 mg/kg/8h have also been trialled as adjunct therapies in the treatment of in refractory childhood epilepsy with promising preliminary results.[64]

5.6 | Dermatological disorders

Several studies have demonstrated a benefit of topical *N. sativa* oil for dermatological disorders including wound healing, eczema, psoriasis and vitiligo.[10,65] *Nigella sativa* extract has also been used to treat moderate to severe gingivitis[66] and chemoradiation-induced oral mucositis in patients with head and neck cancer.[67]

6 | CONCLUSIONS

Nigella sativa and its major constituent TQ have promising anti-inflammatory, antiviral, antioxidant, immunomodulatory and bronchodilatory activities that may allow both to be used in the future as adjuvant therapies to conventional drugs in the management of a diverse number of disease processes. Animal and human studies indicate a good safety profile for *N. sativa* seed oil and TQ. In the quest of efforts to “tune” defensive signals in ways that promote “good” and inhibit “bad” inflammatory responses, TQ seems to be an appropriate candidate. Limitations in the pharmaceutical development of TQ have included strict storage requirements and unfavourable formulation and pharmacokinetic properties such as low oral bioavailability and rapid elimination. Novel developments in nanoparticulate-based oral administration and transdermal delivery may overcome these physicochemical barriers. Clinical development of *N. sativa* and TQ may result in therapies effective for multiple disorders ranging from hypertension, dyslipidaemia, type 2 diabetes mellitus, asthma, osteoarthritis, rheumatoid arthritis, bacterial and viral infections in particular SARS-CoV-2 (Covid 19), cancer, multiple sclerosis and other neurodegenerative disorders,

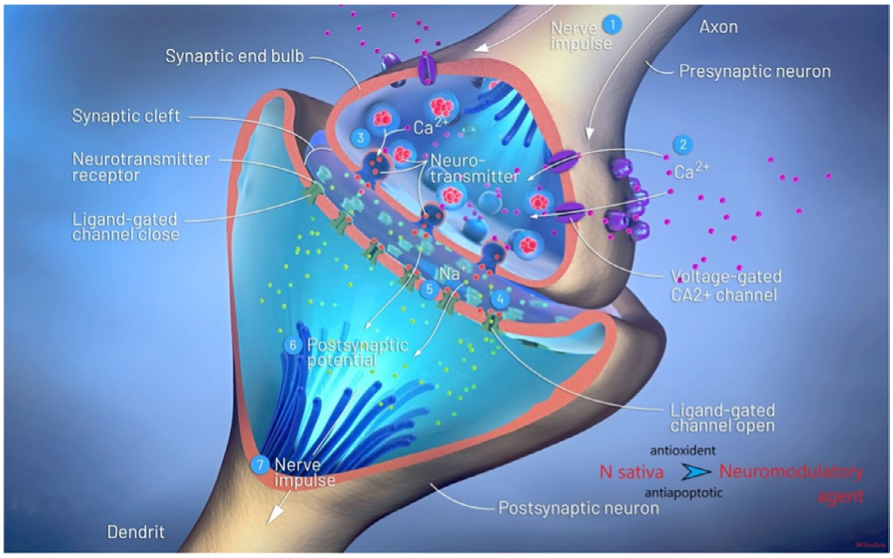

FIGURE 4 *Nigella sativa* and thymoquinone may modulate neurotransmitters such as glutamate and potentially inhibit a cascade that includes calcium influx and release resulting in neurotoxicity and cell apoptosis

epilepsy and dermatological disorders due to its non-specific binding to multiple biological targets. The non-specificity of TQ can be reduced by combining it with the other fractions present in the extract.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this review are available within the article.

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