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REVIEW

Thymoquinone: A Promising Natural Compound with Potential Benefits for COVID-19 Prevention and Cure

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Abstract: COVID-19 has caused a major global health crisis, as excessive inflammation, oxidation, and exaggerated immune response in some sufferers can lead to a condition known as cytokine storm, which may progress to acute respiratory distress syndrome (ARDs), which can be fatal. So far, few effective drugs have emerged to assist in the treatment of patients with COVID-19, though some herbal medicine candidates may assist in the fight against COVID-19 deaths. Thymoquinone (TQ), the main active ingredient of black seed oil, possesses antioxidant, anti-inflammatory, antiviral, antimicrobial, immunomodulatory and anticoagulant activities. TQ also increases the activity and number of cytokine suppressors, lymphocytes, natural killer cells, and macrophages, and it has demonstrated antiviral potential against a number of viruses, including murine cytomegalovirus, Epstein-Barr virus, hepatitis C virus, human immunodeficiency virus, and other coronaviruses. Recently, TQ has demonstrated notable antiviral activity against a SARSCoV-2 strain isolated from Egyptian patients and, interestingly, molecular docking studies have also shown that TQ could potentially inhibit COVID-19 development through binding to the receptor-binding domain on the spike and envelope proteins of SARS-CoV-2, which may hinder virus entry into the host cell and inhibit its ion channel and pore forming activity. Other studies have shown that TQ may have an inhibitory effect on SARS CoV2 proteases, which could diminish viral replication, and it has also demonstrated good antagonism to angiotensin-converting enzyme 2 receptors, allowing it to interfere with virus uptake into the host cell. Several studies have also noted its potential protective capability against numerous chronic diseases and conditions, including diabetes, hypertension, dyslipidemia, asthma, renal dysfunction and malignancy. TQ has recently been tested in clinical trials for the treatment of several different diseases, and this review thus aims to highlight the potential therapeutic effects of TQ in the context of the COVID-19 pandemic.

Keywords: thymoquinone, COVID-19, natural, therapeutic benefits

Introduction

COVID-19 Overview

The novel coronavirus that causes COVID-19 was first discovered in 2019 in Wuhan, China. It has since spread globally, resulting in a worldwide pandemic. COVID-19 is an infectious disease that causes severe acute respiratory syndrome, leading to the virus causing it to be formally named SARS-CoV-2. Comorbidities such as chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients,[1] though the clinical

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features of COVID-19 are varied, ranging from asymptomatic states to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. A fever, coughing, a sore throat, headaches, fatigue, myalgia, and breathlessness are the most common clinical features of COVID-19, however.[2] By the end of the first week, in some patients, the disease may progress to pneumonia, respiratory failure, and death.[3] This progression is generally associated with an extremely uncontrolled production of pro-inflammatory mediators that leads to ARDS and cytokine storm syndrome.[4] Complications thus include acute lung injury, ARDS, shock, and acute kidney injury.

Several clinical trials of possible treatments for COVID-19 are underway, based on those treatments' antiviral, anti-inflammatory, immunomodulatory, antioxidant or similar activities.[5,6] There are also some previously available drugs that have been repurposed for the management of COVID-19, such as remdesivir, hydroxychloroquine, chloroquine, umifenovir, lopinavir, oseltamivir, and favipiravir, as well as adjunctive agents, such as zinc, vitamin D, azithromycin, ascorbic acid, nitric oxide, corticosteroids, and interleukin (IL)-6 antagonists. Growing interest is also developing in the use of new therapeutic methods, such as specific anti-inflammatory molecules (eg tocilizumab), anti-IL-17, and treatment with mesenchymal stromal cells.[7] The amplification of anti-2019nCoV-specific T lymphocytes may be another feasible option for treatment.[8] In terms of prevention, several COVID-19 vaccines are also now available.[9]

Alternative Therapies

Although researchers worldwide have worked exhaustively to find a solution, as yet, no entirely adequate therapy for COVID-19 has emerged. Alternative approaches must thus be subject to comprehensive attention, similar to the strategy used in the initial repurposing of conventional therapeutics. An example of such alternative therapy is found in the application of vitamin D, which has been suggested to help reduce the effect of the pandemic on maternal and child health.[10] Other speculative suggestions include the idea that vitamin C could help with COVID-19-related symptoms,[11] or that honey may have a positive impact on COVID-19 recovery.[12] Pharmacological intervention using natural products is considered another example of alternative medicine.[13]

In the past, herbal medicine has played an important role in managing infectious disease, and a range of herbal medicinal studies on the treatment of a previous SARS coronavirus (SARS-CoV), have provided clinical evidence that herbal medicines have some advantageous effects with regard to the treatment and prevention of epidemics, with several significant results.[14] There is also clinical evidence that the use of herbal medicines can have positive consequences in certain COVID-19 treatments.[15,16] One systematic review has shown significant impacts on efficacy and improvement of symptoms on combining herbal medicine with Western medicine in the treatment of COVID-19, suggesting that herbal medicine does have a potential role to play in COVID-19 treatment. Further clinical trials are, however, necessary to further confirm the efficacy, and any adverse effects, of herbal medicine as part of COVID-19 treatment.[17]

Several edible plants are known to act as natural antiviral agents, and these may have the potential to be developed into a COVID-19 nutraceutical. Such a development may offer a supplementary treatment to help people cope with this highly infectious disease and thus protect the global population against the current pandemic.[18] In terms of daily diet, herbal preparations with immunomodulatory actions may offer prophylactic therapy to prevent infection and to help contain diseases within communities, as well as encouraging faster post-infection healing.[18]

Natural Therapeutic Approaches

Some reports have emerged of the beneficial effects of certain traditional herbal medicines with regard to COVID-19. Examples include Ginseng (*Panax ginseng*), which has a modulatory effect on human immune cells;[19] ginger (*Zingiber officinale*), which has anti-apoptotic, anti-inflammatory, anti-tumor activities, anti-hyperglycemic, antioxidant, and analgesic properties;[20] garlic (Allium sativum), which stimulates the immune system;[21] and Echinacea extract (Echinacea purpurea (L.) Moench), which has antimicrobial and antioxidant activities.[22]

Other herbal phyto-constituents have been reported to be effective in reducing infectious conditions, including triterpene glycosides isolated from *Heteromorpha*[23] and extracts from *Artemisia annua, Lycoris radiata, Pyrrosia lingua and Lindera aggregate*,[17,24] while natural inhibitors such as the nsP13 helicase and 3CL protease have been identified, along with myricetin, scutellarein, and phenolic compounds from *Isatis indigotica* and *Torreya nucifera*, to be operative against SARS-CoV enzymes.[25–27] Moreover, Cinatl et al reported that glycyrrhizin elicited a significant antiviral activity against SARS coronavirus,[28] while *Nigella sativa* (black seed) was reported to have potential for the management of COVID-19 patients' symptoms.[13,29–31]

Nigella sativa: An Overview

Nigella sativa (Black seed), from the family Ranunculaceae, have been found in several ancient sites, including Tutankhamun's tomb. The Persian physician Avicenna, regarded as the father of early modern medicine, described the plant in his Canon of Medicine as offering a treatment for shortness of breath,[32] which frequently accompanies pathological conditions such as asthma and pneumonia. Volatile oils and alkaloids are generally associated with biological activity, and the volatile oils of these seeds contain nigellone, thymoquinone (TQ), thymohydroquinone, dithymoquinone, thymol, carvacrol, α and β-pinene, d-limonene, d-citronellol, p-cymene, carvacrol, t-anethole, 4-terpineol and longifolene.[33,34] *Nigella sativa* seeds thus offer a natural product with multiple potential pharmacological activities including antidiabetic, anticancer, immunomodulatory, analgesic, antimicrobial, anti-inflammatory, bronchodilator, renal and gastro-protective, and antioxidant properties.[35,36]

Thymoquinone

Thymoquinone (2-Isopropyl-5-methylbenzo-1, 4-quinone) is the main active ingredient of the volatile oil of black seed (Figure 1). It was first extracted by El–Dakhakhny,[37] and amongst the various different active constituents reported so far, TQ remains the major bioactive principle due to its range of therapeutic benefits including antioxidant,[38] anti-inflammatory,[39] anti-cancer,[40] antibacterial,[41] antifungal activity,[42] and anticonvulsant activity.[43] Furthermore, a more specific effect of the antiviral activity of TQ and black seed fixed oil against murine cytomegalovirus infection model has been reported.[44,45] TQ may thus offer integral complementary support in conditions of uncertain core basic needs during COVID-19 treatment. However, the question of whether TQ might act as a distinct therapeutic drug for the control and/or treatment of COVID-19 still remains to be investigated.

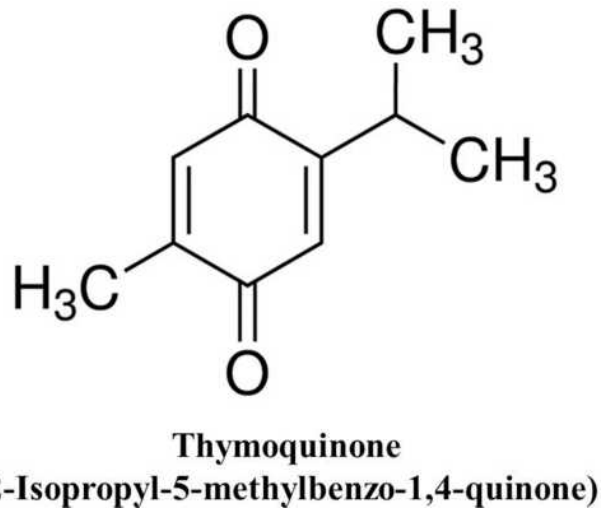

Figure 1 Chemical structure of thymoquinone.

The Aim of the Review

This review aims to focus on the potentially beneficial roles of TQ against COVID-19 pathophysiology in the context of antioxidant, anti-inflammatory, immunomodulatory, epigenetic modulation, antiviral activity, docking studies on anti-COVID-19 activity, antibacterial and anticoagulant effects for the treatment of COVID-19.

Potential Beneficial Effects of Thymoquinone in COVID-19

N sativa, due to its wide range of bioactive components such as TQ and nigellimine, could offer a range of benefits for treating COVID-19, such as blocking the introduction of the virus to pneumocytes; providing ionophores to improve zinc intake, thereby improving the host immune response to SARS-CoV-2; and preventing the virus from replicating.[29] TQ is the main bioactive principle in *N Sativa*, and this has been found to confer a range of therapeutic advantages[34] including antioxidant,[38] anti-inflammatory,[39,46] anticancer,[40] antibacterial,[41] antifungal,[42] anticoagulant,[47] anti-sepsis,[48] and anticonvulsant activity.[43] *N Sativa* seeds have also demonstrated immunomodulatory effects,[49,50] while several studies suggest that *N Sativa* seeds have some antiviral effects.[44,51,52] In addition to its immunomodulatory and antioxidant properties, however, *N Sativa* and its active constituents have also been noted to provide anti-ischemic effects in several organs, including the brain, kidney, heart, liver, and intestines.[53] Such evidence strongly suggests that *N. sativa* seeds and their active constituents may have significant therapeutic potential against COVID-19 and its complications[13,54] (Figure 2).

Antioxidant Effect

Reactive oxygen species (ROS) are formed during normal cellular respiration and as a reaction to xenobiotics.[55] They are highly reactive, and thus may harm and change the functions of various cell components, such as lipids, proteins, nucleic acids, and carbohydrates.[56] Oxidative stress occurs due to imbalance between oxidants and antioxidants,[57] and it is a crucial factor in pathogenesis of many diseases[58] such as diabetes,[59] inflammation,[60] cardiovascular diseases,[61]

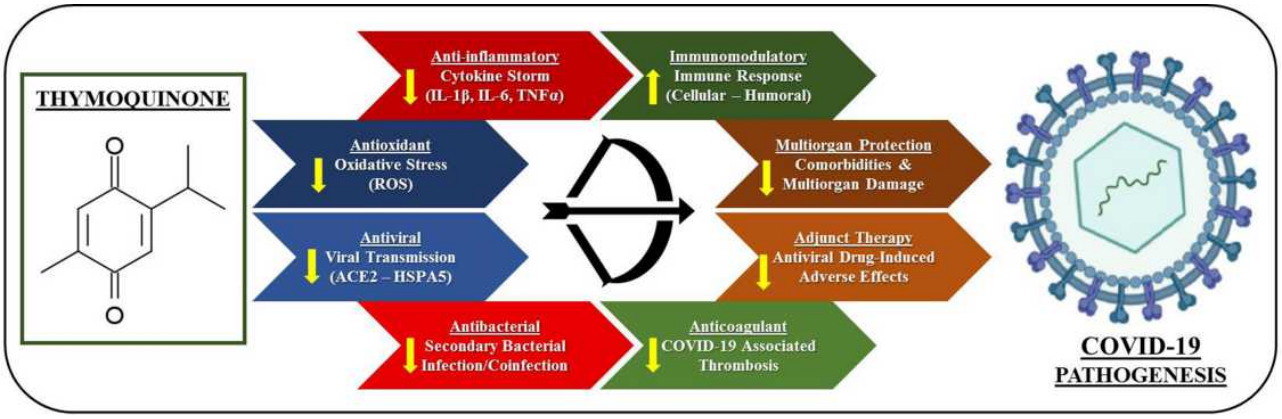

Figure 2 Multitargeted protective effects of thymoquinone against COVID-19 pathogenesis.

cancer,[62] and advanced age.[63] A major factor in the excessive immune response seen in some COVID-19 infections may thus be the overwhelming of the antioxidative defense mechanism and the resulting oxidative damage.[55]

Antioxidant properties require high radical-scavenging capabilities, and this is one of the essential characteristic functions of TQ. TQ works by activating the enzymes that protect cells from cellular damage caused by oxidative stress. Several studies have shown that TQ does this by increasing the expression of mRNA and stimulating various cytoprotective antioxidant enzymes, including catalases, superoxide dismutase, glutathione reductase, and glutathione-S-transferase.[64–68] TQ thus offers protection against glucose or methylglyoxal induced loss of superoxide dismutase activity and fragmentation or cross-linking.[69]

Anti-Inflammatory Effect

While the rapid spread of COVID-19 is concerning, the inflammatory response of the host is an important determinant of the outcome and severity of any infection.[70] A cytokine storm represents cytokine overproduction, seen in the most severe cases of COVID-19, a process which includes T cell depletion, pulmonary disease and damage to the lungs.[71] Granulocytosis can also lead to strong superoxide explosion,[72] the formation of reactive oxygen species (ROS)[73] and further production of proinflammatory cytokines.[74] The background of anti-inflammatory therapy complementing antiviral therapy must thus be understood in order to manage such symptoms in COVID-19, as treatment should aim to control inflammation without affecting the host's ability to respond adaptively to the virus. The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) can resist oxidative stress,[75] and this is always dysregulated in disease states, such as diabetes, liver disease, and inflammatory bowel diseases,[76] as well as in severe aging.[77] Any such conditions are thus risk factors for COVID-19-induced ARDS.[78]

Activation of Nrf2 has also been shown to be involved in preserving lung architecture in reactions to inflammatory syndrome, as well as having some therapeutic effects in various lung disorders, including respiratory infections and ARDS.[79] Furthermore, Nrf2 is responsible for the transcription of certain macrophage-specific genes involved in the tissue repair that grant protection from viral infections,[80] as well as restoring redox homeostasis, which protects against oxidative stress by upregulating thioredoxin reductase, glutathione, peroxiredoxin, and NADPH.[81]

It has been reported that TQ decreases levels of various proinflammatory mediators, such as IL-1β, IL-6, TNFα, IFNβ, and PGE[66] in rats, as well as preventing pulmonary inflammation and improving the resistance of airways to damage induced by diesel exhaust particles. TQ also decreases blood leukocyte and plasma IL-6 levels.[82] In a mouse model of allergic asthma, TQ reduced lung eosinophils, increased Th2 cytokines, and decreased mucus-producing goblet cells.[46] TQ also inhibits inducible synthase nitric oxide (iNOS) and transforming growth factor-β1 in asthmatic murine experimental models.[83–85]

The experimental evidence suggests that TQ inhibits cyclooxygenase (COX) and lipoxygenase enzymes, preventing the generation of eicosanoids.[86] TQ decreases the synthesis of LTs[87] and inhibits prostaglandin and thromboxane synthesis by decreasing COX2 expression, achieved by upregulating IL-1 receptor-associated kinase 1 (IRAK1).[88] IRAK1-mediated signal inhibitors also

downregulate NF-κB and activator protein 1/AP1 transcriptional activities which are required to activate the COX-2 expression,[88] and TQ further downregulates the expression of many other inflammatory cytokines and signals mediators, including interleukin IL-1, IL-6, TNFα, and iNOS.[88] These mediators can cause alveolar macrophages and neutrophils to create more damage by increasing pulmonary vascular permeability, releasing oxygen radicals and proteolytic enzymes.[89] The antioxidant activity of TQ can also help in minimizing cell inflammation, while its ROS generation plays an important role in the synthesis of arachidonic acid based on the activation and/or expression of the basic upstream signaling molecules protein kinase B and NF-κB.[90]

Immunomodulatory Effect

TQ has several major immunomodulatory effects due to the crosslink between inflammatory and immunomodulatory pathways. TQ could thus potentially suppress inflammation-induced immunosuppression based on its negative effects on proinflammatory eicosanoid synthesis and mediated gene expression in NF-κB.[91] TQ can thus modulate many aspects of cellular and humoral immunity by inhibiting the function and expression of various inflammatory cytokines and their effector molecules.[92] TQ modulates cell immune responses, including dendritic cell maturity, NK-cells cytotoxicity, phagocytic involvement, chemotaxis, and the activation of T-cells. It also tends to have a context-relating effect on particular cell immune responses: for example, TQ prevents the maturation of lipopolysaccharide-induced dendritic cells by blunting the expression of IL-10, IL-12 and TNFα with enhancement of caspase 3/8 and increasing annexin V binding.[93] TQ also improves the survival of CD8 antigen-specific T cells and improves the sustained expression of L-selectin, which may have an important effect on adoptive T cell therapy.[94]

Epigenetic Modulatory Effect

Various epigenetic pathways are involved in COVID-19 infection, and these pathways may thus be therapeutically utilized.[95] Possible targets for host immune response include epigenetic enzymes.[96,97] The aberrant genetic expression and protein function that characterize COVID-19 are caused by genetic and epigenetic changes, and natural compounds can target and regulate genetic expression, directly or indirectly, based on their interference with genetic and epigenetic mechanisms.[98–100] TQ is thus a promising molecule because it modulates epigenetic properties such as histone acetylation and deacetylation as well as DNA methylation and demethylation.[101,102] In addition, TQ plays a role in activating and deactivating noncoding RNA, acting as a potent apoptosis-induced enzyme that causes histone acetylation and deacetylation.[103–105]

Endogenous miRNA activity has been studied in the field of viral replication for several complex virus mechanisms.[106] It has thus been shown that miR34a has an effect on the inactivation of epithelial-mesenchymal transition-transcription factors (EMT-TFs), and epithelial–mesenchymal transition is known to play a crucial role in organ fibrosis and epithelial cell malignancy.[107] A promising therapeutic approach against COVID-19 thus stems from the idea of inactivating EMT-TFs using miR34a,[108] as a previous study showed that TQ may act as an enhancer of miR34a activity.[109] miR146a is another miR involved in the process of inflammatory cytokine inhibition, which acts via the NF-κB pathway.[110] It functions as a negative regulator for NF-κB, and it is a well-recognized transcript factor for the IL-6 gene.[111] miR-146a-5p transcription is also regulated by NF-κB,[112] and patients with COVID-19 have been shown to have higher levels of IL-6 and lower levels of miR-146a-5p than average, suggesting imbalances in the physiological axis of IL-6/miR-146a-5p in the pathogenesis of COVID-19 infections.[113] TQ treatment, however, controls miR146a expression and can therefore reduce inflammatory reactions by interfering with NF-kB.[114]

Antiviral Activity

Several studies support the potential antiviral activity of TQ against various viral infections, which is mainly attributed to its multiple beneficial effects, such as antioxidant, anti-inflammatory, and immunomodulatory effects in addition to possible direct viral eradication.[115,116] The antiviral effect of *Nigella sativa* oil, including its major active component TQ, was demonstrated in a murine cytomegalovirus (MCMV) model; this showed that *Nigella sativa* significantly reduced the liver and spleen viral loads, which coincided with enhanced IFN-γ production and increased CD4 (+) T cell response.[44] TQ has also been shown to significantly inhibit *Epstein-Barr* virus (*EBV*) replication in EBV-infected B cells,[117] while *Nigella sativa* has been shown to exhibit antiviral activity against the hepatitis C virus (HCV), as evidenced by reduced viral load and improved liver function in HCV patients who received Nigella sativa at 450 mg, three times a day for

three successive months.[51] This effect is also supported by observations of the selective inhibition of HCV virus replication by alpha-zam, a *Nigella sativa* seed formulation.[118] *Nigella sativa* has also been suggested to be effective in controlling human immunodeficiency virus (HIV) infection, with one study reporting that treatment of HIV patients with *Nigella sativa* for six months resulted in sustained sero-reversion with a significant reduction in viral load and CD4 count elevation.[52]

Nigella sativa extract containing TQ has also, more specifically, been reported to decrease viral replication and loads in cells infected with some coronaviruses.[119] Interestingly, one in vitro study demonstrated that TQ showed significant antiviral activity against a SARSCoV-2 strain isolated from Egyptian patients,[120] possibly through blocking the entry of the virus into the cells.[121] Overall, the existing studies highlight the immense potential of TQ as an effective antiviral agent against COVID-19, a premise which is highly supported by the molecular docking studies examining TQ's effects against various virus and host cell targets, which are discussed in more detail in the following section.

Molecular Docking Studies Related to Anti-COVID-19 Activity

Molecular docking is a promising in silico method that may be used to screen various compounds for their antiviral potential by testing the binding affinities of the compounds against different viral or host cell receptor proteins. The molecular targets of SARS-CoV-2 include various viral proteins involved in viral entry, such as spike proteins, and replication, such as viral proteases.[122] In addition, host cell targets, such as angiotensin-converting enzyme 2 (ACE2) receptor and cell surface heat shock protein (HSPA5), which are involved in viral entry, may also offer potential therapeutic targets.[122] Molecular docking studies have already shown that TQ could potentially inhibit COVID-19 by binding to the receptor-binding domain on the spike protein of SARS-CoV-2, which would hinder virus entry into the host cell.[123] Additionally, it may bind to the SARS-CoV-2 envelope protein and inhibit its ion channel and pore formation activity.[124] Other studies have shown that TQ might display inhibitory action against the SARS CoV2 protease, which would halt viral replication.[120,125–127]

TQ has also demonstrated a good affinity against ACE2 receptors, which allows it to interfere with virus uptake into the host cell.[121,127] Molecular dynamics simulations have shown that TQ can interfere with the attachment of SARS-CoV-2 to host cells by binding to a cell surface, HSPA5, which is recognized by the viral spike protein and upregulated upon viral infection.[128,129] These in silico studies indicate a multi-targeted potential for TQ against COVID-19, and thus pave the way for further investigation of such anti-COVID-19 potential through in-vitro and in-vivo studies that may better support translation into clinical practice.

Antibacterial Activity

COVID-19 may also be associated with serious secondary bacterial infections, such as bacterial pneumonia, as well as nosocomial infections resulting from the prolonged hospitalization of critically ill patients, both of which significantly increase morbidity and mortality in COVID-19 patients.[130] Moreover, the intensive use of antibiotics in patients suffering from COVID-19 could result in the emergence of multidrug-resistant bacteria, which could further worsen COVID-19 adverse outcomes.[131] Interestingly, TQ exerts antibacterial activity against several Gram positive and Gram negative bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*, which could be used to augment antibiotic effects.[41,116,132] Furthermore, TQ has demonstrated significant antimicrobial activity against anaerobic bacteria, specifically *Clostridium difficile*,[133] as well as clinical isolates of *Mycobacterium tuberculosis*,[134] alongside antibacterial and resistance modifying activities with regard to methicillin-resistant *Staphylococcus aureus* (MRSA)[135] and *Listeria monocytogenes*.[136]

Nigella sativa was also seen to be significantly effective in eradicating *Helicobacter pylori* in patients with non-ulcer dyspepsia.[137] This suggests that TQ could play a significant role in the prevention and management of secondary bacterial infections in COVID-19 patients in addition to its potential value for modifying bacterial resistance and potentiating antibiotic actions.

Anticoagulation Effect

Thrombotic complications have become a major problem in COVID-19 patients. Preliminary COVID-19 studies have shown that infected patients typically develop thrombocytopenia with higher D-dimer levels, while the rates of

developing thrombocytopenia in patients with severe COVID-19 are even higher.[70] Viral infections often cause systemic inflammatory responses and interfere with the balance of procoagulants and anticoagulants,[138] and in severe or critically ill patients, large quantities of inflammatory mediators, hormones and immunoglobulin are released, leading to blood hypercoagulability. The level of interleukins, especially IL-6, IL-7, IL-2, granulocyte colony-=stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory proteins 1-alpha, and TNFα, has been similarly found to be increased in patients with COVID-19.[139]

An earlier study found that coagulation factors VII, VIII, II, V, and X were significantly increased in COVID-19 patients.[140] TQ, however, interferes with blood clotting by directly decreasing factor Xa activity in the blood coagulation pathway and by down-regulating TNFα, a cytokine that plays a critical role in the link between inflammatory and thrombosis pathways.[47]

The Effect of Thymoquinone on Comorbidities

The magnitude of COVID-19 infection is increased by a variety of comorbidities. TQ may thus also be helpful in patients infected with COVID-19 where it can relieve some comorbidity.[13] Serious COVID-19 complications include ARDS, pneumonia and multi-organ failure, and the risk of all of these is increased in patients with diabetes and cardiovascular diseases.[141,142] N. Sativa has been shown to reduce plasma glucose levels and control haemoglobin-A1c,[143] while intraperitoneal administration of TQ has been demonstrated to substantially decrease hyperglycemia in streptozotocin-induced diabetes in the rats.[144] One study reported that 7% of deaths in COVID-19 patients can be ascribed to circulatory failure in myocarditis, suggesting that cardiovascular disorders play an important role in determining final adverse outcomes.[145] TQ can also act centrally as an antihypertensive agent, as well as having a regulatory effect on platelet aggregation and blood clotting,[146,147] and TQ protects the heart from injury induced by isoproterenol in rats.[148]

It is also notable that autoimmune and auto-inflammatory diseases, especially in children, may impact the severity of COVID-19 infection, with overlapping symptoms leading to pediatric inflammatory multisystem syndrome (PIMS) that includes Kawasaki-like diseases.[149,150] This complex syndrome has been reported as "Kawa-COVID-19" because of the association with the symptoms of COVID-19 infection.[151,152] In patients with Kawa-COVID-19, C-Reactive protein (CRP), IL-6, IL-8, and TNF-α were all significantly raised,[153] suggesting that *Nigella sativa* could play a beneficial role in controlling incidence of PIMS or Kawa-COVID-19 by regulating and modulating immune response and reducing the occurrence of proinflammatory cytokines IL-2, IL-4, IL-5, II-6, IL-12, and IL-13.[154]

Dual Benefit of Thymoquinone as Adjunctive Therapy

TQ can be used in combination with other therapeutic agents that may be usefully repurposed for the treatment of COVID-19, as well as alongside other supportive treatments. Given the multiple beneficial effects of TQ and its favorable safety profile,[155] the adjunct use of TQ with conventional therapeutic agents would have the dual benefit of attenuating drug-induced toxicity and improving therapeutic effectiveness, which could in turn result in reducing the required effective dosage of concomitantly used drugs, thus further minimizing any adverse effects. The potential cardioprotective,[156] neuroprotective,[157] hepatoprotective,[158] nephroprotective,[159] and gastroprotective[160] effects of TQ may thus be employed in counteracting a range of drug-associated toxicities;[161] currently, various supportive treatments such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) render COVID-19 patients at increased risk of liver and kidney toxicity.[162,163]

TQ has been shown to counteract acetaminophen-induced hepatotoxicity[164,165] as well as NSAIDs-associated nephrotoxicity and gastrointestinal side effects.[166] TQ can also act synergistically with corticosteroids to protect the lungs by mitigating the inflammatory response and resulting cytokine storm; this would allow the use of lower steroid doses, thus reducing the risk of potential adverse effects.[167,168] TQ has further demonstrated significant protective effects against the renal toxicity associated with antibiotics, such as vancomycin used in COVID-19 patients with secondary bacterial respiratory infections.[169] TQ could also potentially counteract the toxic effects of various repurposed drugs,[170,171] such as the cardiotoxicity risk associated with chloroquine and azithromycin[161,172,173] and the potential liver and kidney toxicities associated with antivirals such as remdesivir and lopinavir.[155,161,170] TQ can also exert gastroprotective

effects[160] against gastric ulceration, which is associated with the IL-6 antagonist, tocilizumab,[174] in addition to potentiating its anti-inflammatory effect.[175]

Clinical Applicability of Thymoquinone

The high hydrophobic and lipophilic characters of TQ lead to poor solubility, low bioavailability, and difficulty in formulation.[176] The various pharmacokinetics of TQ have been reported in detail,[177–179] and TQ has poor oral bioavailability based on its low aqueous solubility and dissolution rate.[180] Moreover, TQ shows rapid polyexponential decline following intravenous dosing,[178] as well as binding with bovine serum albumin and alpha-1 acid glycoprotein.[181–183] This poor solubility and limited bioavailability are the two main problems for developing TQ for clinical use, and several chemical derivatives and novel nanoformulations have thus been developed to improve the pharmacokinetic behaviors of TQ to increase bioavailability.[184,185] TQ has, for example, been successfully encapsulated into nanolipid carriers.[186–188]

TQ in different dose ranges shows beneficial effects with negligible toxicity in animal models of different diseases.[156–159,189–195] TQ is a well-tolerated drug in rodents, and numerous studies have been done to determine the toxicological properties of TQ in vitro and in vivo.[196–198] Even mice treated with 0.03% TQ in their drinking water for three months showed no signs of toxicity.[196] Moreover, TQ has demonstrated a high safety profile in rats based on high doses using oral and intraperitoneal administration.[199,200]

TQ compounds are currently used in clinical trials for the treatment of various types of cancer and other diseases.[201,202] In a Phase I safety and clinical activity study of TQ in patients with advanced refractory malignant disease, TQ was well tolerated at doses ranging from 75 mg/day to 2600 mg/day, with neither toxicities nor therapeutic responses reported.[203] This absence of side effects in humans is in agreement with the extremely low toxicity of oral TQ administration in experimental animals.[196]

Prospects and Limitations

Despite the numerous molecular docking studies on potential anti-COVID-19 activity of TQ, experimental studies on the effects of TQ against COVID-19 and its associated complications remain limited. The multi-targeted beneficial effects of TQ and its favorable safety profile do, however, appear to warrant in-vivo investigations and clinical trials on its anti-COVID-19 potential to support the translation into clinical practice to treat COVID-19 patients either alone or in combination with other potential therapies. TQ could also provide the additional benefits of ameliorating comorbidities and attenuating certain drug-induced adverse effects, as well as improving the therapeutic effectiveness of some other therapies. Novel formulations of TQ nanoparticles may, however, be required to overcome the poor bioavailability and the pharmacokinetic limitation of this compound in terms of clinical use.

Conclusion

This article examined the concept that certain natural compounds may target the molecular mechanisms of COVID-19, as well as potentially assisting with overcoming the diverse health complications associated with the repeated use or withdrawal of conventional therapeutics. TQ, the main active ingredient of Black seed oil, is an easy, cost-effective natural source of anti-inflammatory, antioxidant, immune stimulant, antibacterial, anticoagulant, and antiviral properties. TQ use may thus be expected to improve COVID-19 comorbidities and to protect against certain antiviral drug-induced side effects and toxicities. TQ appears to be a promising therapeutic option for managing COVID-19 and its complications, and clinical trials in COVID-19 patients to examine the beneficial effects of TQ are thus highly recommended.

Abbreviations

ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease-2019; COX, cyclooxygenase; EBV, Epstein-Barr virus; EMT-TFs, epithelial–mesenchymal transition–transcription factors; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSP, heat shock protein; IL, interleukin; IRAK1, interleukin-1 receptor-associated kinase 1; MCMV, murine cytomegalovirus; Nrf2, the nuclear factor erythroid 2 (NFE2)-related factor 2; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome; TQ, thymoquinone.

Disclosure

The authors report no conflicts of interest in this work.

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