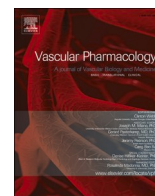




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The potential role of thymoquinone in preventing the cardiovascular complications of COVID-19

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ABSTRACT

A new virus strain detected in late 2019 and not previously described in humans is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes corona virus disease (COVID-19). While potential therapeutic approaches for COVID-19 are being investigated, significant initiatives are being made to create protective drugs and study various antiviral agents to cure the infection. However, an effective treatment strategy against COVID-19 is worrisome inadequate. The objective of the present manuscript is to discuss the potential role of thymoquinone (TQ) in preventing the cardiovascular complications of COVID-19, focusing on viral inhibition, antioxidant potential, vascular effect, and cardiac protection. The multifunctional properties of TQ could potentially synergize with the activity of current therapeutic interventions and offer a basis for managing COVID-19 disease more effectively. Even though the experimental evidence is positive, a translational application of TQ in COVID-19 is timely warranted.

1. Introduction

The newest severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) and its associated corona virus disease (COVID-19) were identified in late 2019 in Wuhan, China. The virus was declared as a pandemic on March 11th, 2020. As of June 7, 2021 COVID-19 has had a worldwide effect on the lives of over 173 million people [1]. The SARS-CoV-2 infection is initiated via inoculation of the airway mucosa with the help of the angiotensin converting enzyme 2 (ACE-2) receptor, which acts as a functional receptor for cell entry. This contributes to the development of pneumonia and cardiovascular complications in COVID-19 patients. Since ACE-2 is the functional receptor for the infection, attention has been given to the protective and therapeutic effectiveness of drugs that can interfere with or modulate this pathway. In this review, we summarize the potential role of thymoquinone (TQ) in preventing and/or ameliorating the cardiovascular complications of COVID-19.

2. ACE-2 and SARS-CoV-2

Epithelial cells of the intestines, kidney, lung, blood vessels, and heart mainly express ACE-2 receptors [2,3]. ACE and ACE-2 perform different physiological functions; ACE cleaves angiotensin (AT)-I to AT-

II, which in turn binds and triggers the AT-II type-I receptor. This activation further results in pro-oxidative, pro-inflammatory, and vasoconstrictive effects [3]. On the other hand, ACE-2 converts AT-II to AT (I-VII), which works on the Mas receptor (MasR) to control the blood pressure while also reducing inflammation and fibrosis [4]. More precisely, AT (I-VII) is known to enhance vasodilation and water and sodium excretion, increase nitric oxide synthesis and decrease sympathetic nervous system tone [5,6]. Therefore, ACE-2 is one of the most essential regulators of blood pressure, inflammation, and fibrosis, which contribute is substantial in the pathophysiology of hypertension, cardiovascular illness, and chronic kidney disease [7]. Coronavirus can trigger a severe acute respiratory syndrome (SARS) through interaction with ACE-2 cellular receptors to mediate target cell infection [8,9]. SARS-CoV-2 primarily attacks the epithelial cells of alveoli, inducing signs and symptoms in the respiratory tract [10,11]. These effects are more serious in patients with cardiovascular disease (CVD); this could be due to high ACE-2 expression in such patients relative to healthier individuals. Since ACE-2 role is essential, it is important to carefully consider the efficacy and therapeutic potentials of antihypertensive drugs such as AT receptor blockers and ACE inhibitors in patients with COVID-19 [11]. ACE-2 may further be associated with the mechanism of acute myocardial damage caused by SARS-CoV-2. In addition to the

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lungs, ACE-2 expression in the cardiovascular system mediates the signaling mechanisms of cardiac injury. Another potential form is related to the cytokine storm, which occurs during myocardial injury and is elicited by an imbalanced response of the T-helper cells type-1 and 2, as well as in respiratory impairment and hypoxemia [12,13]. Majid and co-workers stated that COVID-19 can pose devastating threats to people with chronic CVD and may induce cardiac failure even in individuals without existing heart problems [14]. Generally, the cardiac muscle damage may occur in any patient with or without heart failure but the incidence is greater in patients with pre-existing heart disease. The report further clarifies the results of previous studies on epidemics of coronavirus and influenza, which indicated that virus infections may elicit arrhythmias, acute coronary syndrome, and heart failure progression or exacerbation [15–18]. Moreover, among known cases of SARS-CoV-2 infection identified by the National Health Commission (NHC) of China, some of the patients were first seen due to cardiovascular symptoms. The subjects reported palpitations of the heart and tightness of the chest rather than respiratory infection signs such as cough and fever were subsequently identified with COVID-19 [11]. Of those who died from COVID-19, approximately 12% of patients without existing CVD had significant cardiac injury, with higher rates of cardiac troponin I or heart failure during hospitalization [11]. In fact, the cardiac difficulties in patients with COVID-19 are thought to be due to severe a systemic inflammatory response and immune dysregulation during of the infection.

3. Thymoquinone (TQ) and COVID-19

Virus entry intervention can be an important clinical technique to avoid viral infection. The development and usage of enfuvirtide, a peptide-based medication that prevents the entrance of HIV by attacking the Gp41 portion of the HIV surface glycoprotein (equivalent to S2 in SARS-CoV-2) has provided proof of theory [19,20]. The SARS-CoV-2 S protein is highly conserved across all human coronaviruses (HCoVs) and plays a role in receptor identification, viral attachment, and host cell invasion. In fact, it is one of the most significant targets for COVID-19 drugs and vaccines due to its essential role [21]. As regards to global morbidity and mortality, CVD imparts a significant burden on health-care systems [22,23]. COVID-19 exerts oxidant tension in the cardiovascular system [24,25]. This oxidative stress arises in the myocardium coincides with a ventricular dysfunction. Reactive oxygen species (ROS), which adversely influence the processing of myocardial calcium, induce dysrhythmias and lead to heart remodeling by causing hypertrophy, apoptotic changes and necrosis [26]. Likewise, a variety of pro- and antioxidant mechanisms that integrate region-specific ROS development and elimination closely control oxidative balance in the vasculature. ROS often mediate several vascular cell functions including the development, migration, and proliferation of smooth muscle and endothelial cells, vascular tone, genomic stability, apoptosis, angiogenesis and host defenses [26,27]. However, excessive amounts of ROS facilitate vascular dysfunction by direct and permanent oxidative harm, as well as deprivation of vascular tissue signaling mechanisms that are based on redox cycling [26,28,29]. Considering that the role of AT-II is critical in the upstream cause of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase ROS formation, angiotensin receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEIs) that exert their beneficial therapeutic effects in part via antioxidant mechanisms [30]. Indeed, ACEIs effectively mitigate inflammatory activities in the vessel wall [31], deter vascular smooth muscle cells (VSMCs) proliferation, and in particular vascular and phagocytic NADPH oxidase activation [31,32]. The decreased oxidative stress avoids superoxide anions from decaying nitric oxide (NO) and inhibits vasoconstriction and pro-inflammatory reactions. Therefore, ACEIs may be considered a key therapy preventing the development of ROS at the enzymatic root [32].

A multi-center, randomized controlled trial was recently conducted in COVID-19 patients treated with an alternative therapy. The patients

received honey and *Nigella sativa* (*N. sativa*) at 1 g and 80 mg kg⁻¹ d⁻¹, respectively, or placebo up to 13 days of infection. The findings of the trial indicate that honey and *N. sativa* usage facilitates viral clearance in patients with COVID-19 and decreases the seriousness of the disease. The positive outcomes of treatment were especially promising because of the very strict eligibility criteria, which included excluding asymptomatic as well as moderate symptoms patients. These findings are consistent with the antiviral, anti-inflammatory, and immune properties of honey and *N. sativa* (NIH Clinical Trial Register number: NCT04347382). Furthermore, it has been proposed that *N. sativa* constituents might offer benefits in the treatment of COVID-19, which include blocking the entry of the virus, enhancing Zinc immune effect against SARS-CoV-2 as well as inhibiting viral replication [33].

TQ is the main active constituent of *N. sativa* (black seed) that demonstrated various biological activities such as cardioprotective, anti-fibrotic effect, anti-inflammatory, immunomodulatory, and antioxidant and anti-apoptotic properties [34,35]. In particular, TQ has been found to be effective in reducing the cytokine storm and improving outcomes of sepsis [36–38]. Other potential effects of TQ include activity against avian influenza virus (AIV H9N2) and murine cytomegalovirus; this anti-viral action is mediated by enriching the antibodies titer against AIV H9N2 and decreasing coronavirus replication [39–42]. TQ may too inhibit SARS-CoV-2 binding to ACE-2 receptors and therefore prevent virus entry and replication [43–45]. The potent anti-oxidant action of TQ can inhibit non-enzymatic lipid peroxidation and cause vasodilation [46,47]. TQ has also been shown to prevent hypertension and renal damage of N-nitro-L-arginine methyl ester in rats [48,49]. Endothelial dysfunction promotes the initiation and development of major cardiovascular diseases such as atherosclerosis and hypertension. TQ improves/repairs the endothelial function through inhibition of oxidative stress and normalization of the angiotensin system [50]. Earlier studies indicated the implication of the AT system in endothelial dysfunction of the aging process [51]. TQ treatment has been found to normalize the expression level of calcium-activated potassium channels (i.e., SKCa and IKCa), endothelial nitric oxide synthase (eNOS), oxidative stress, and the AT system in rats [37,50]. The effects of TQ were also associated with reduced NADPH oxidase-dependent superoxide production and reduced angiotensin network in cells [34,52–55]. Furthermore, TQ has been shown to inhibit AT-II-induced vascular SMCs proliferation and migration through an AMPK/PPAR γ /PGC-1 α mechanism [56]. TQ can also protect heart against ischemia/reperfusion (I/R) injury, which is associated with anti-oxidative and anti-apoptotic effects through activation of autophagy [57]. Interestingly, the activation of Nrf2/HO-1 pathway can improve coronary microembolization (CME)-induced cardiac dysfunction effectively and reduce myocardial apoptosis [58]. Given this, TQ was found to activate Nrf2/HO-1 pathway as well [35,59].

Collectively, the beneficial potential of TQ in CVD is thought to be due to its capacity to activate endothelial cells to surge the production of NO and endothelium derived hyperpolarizing factor (EDHF), reduce the endothelial formation of vasoconstrictive factors (e.g., Thromboxane A2), and also its effect on vascular SMCs to decrease oxidative stress. Thus, the actions of TQ on the endothelium and SMCs may promote vascular health in COVID-19 patients and could potentially reduce the morbidity and mortality of the disease (Fig. 1).

4. Conclusion

Possible therapeutic approaches for COVID-19 are being investigated, and significant initiatives are being made to create protective measures and study antiviral drugs to cure the disease. However, an effective treatment strategy against COVID-19 is worrisome lacking. Here we propose that TQ may help to prevent the cardiovascular complications of COVID-19. The multifunctional properties of TQ could potentially synergize the activity of the current therapeutic interventions and offer a basis for managing COVID-19 disorders including multifactorial pathogenesis, and hence, allowing for a strategy of several

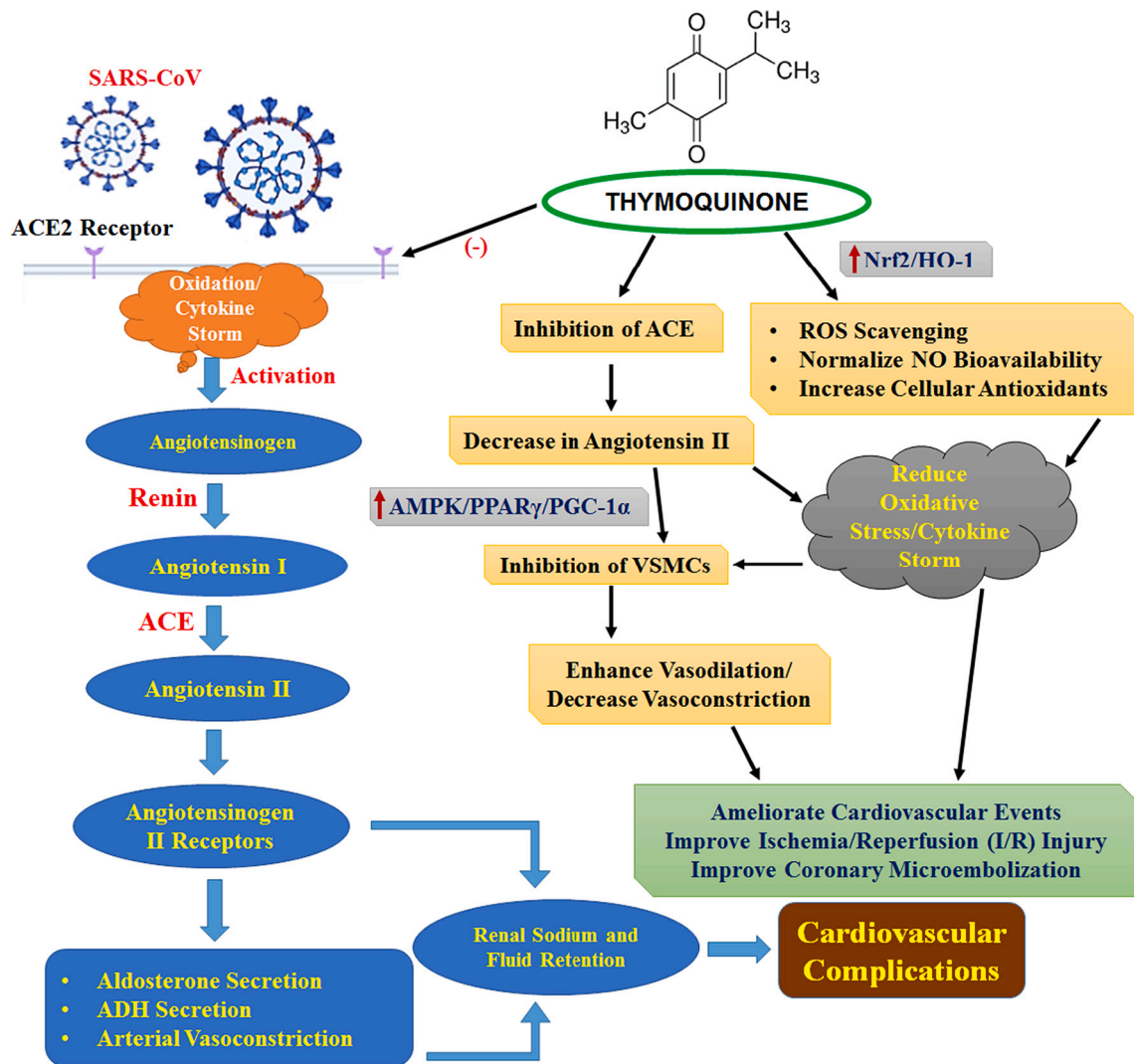


Fig. 1. Schematic illustration of SARS-CoV induced cardiovascular complications and thymoquinone potential inhibitory effects on viral infection and amelioration of cardiovascular events. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE, angiotensin converting enzyme; ADH, antidiuretic hormone; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, Heme oxygenase-1; AMPK, activated protein kinase; PPAR, peroxisome proliferator-activated receptors; PGC-1 α , peroxisome proliferator-activated receptor gamma co-activator 1alpha; ROS, reactive oxygen species; NO, nitric oxide; VSMCs, vascular smooth muscle cells; (–) indicates inhibition; (upward arrow) indicates upregulation.

aims [60–62]. Although the experimental indications are encouraging, there is an opportune need to explore the translational features of TQ in COVID-19.

Author statement

A.A., K.M.A. conceptualization and drafted the manuscript. A.A and M.R. prepared figure. K.M.A and A.A. edited and revised the manuscript. All authors approved the final version of manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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