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Review Article

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The Role of Quercetin in Ameliorating ARDS in COVID-19 Patients

Saurabh Sharma, DO, MS and Anand Seth, PhD*

SK Patent Associates LLC, Dublin, Ohio, USA

Abstract

The sudden outbreak of a novel coronavirus in December 2019 in Wuhan, China, known as Covid-19, spread throughout the world as a global pandemic. An immediate search started throughout the world to combat the virus on various fronts. Many clinical trials were initiated and are underway to utilize the existing drugs to delineate and combat virulence of the virus. Several vaccines have been developed and are under development including various combinations of herbal remedies. Molecular docking studies have shown that bioactive compounds like Quercetin found in medicinal plants have the best potential to act main protease inhibitor which in turn can help fight the virus. Quercetin improves arterial blood gas, lung water content, protein content, and cell count in bronchoalveolar lavage (BAL). ARDS-related mortality is high among Covid-19 patients. Quercetin can potentially serve as a potent supplement for the group of people who are infected with Corona-19 virus and predisposed to acute respiratory distress syndrome (ARDS), ARDS is one of the major causes of mortality in SARS-CoV-2 / Covid-19 infected patients.

Introduction

COVID-19 and ARDS

December 2019 was the first time a case of COVID-19 was identified in Wuhan, China, and ever since the virus has spread throughout the globe-spanning 222 countries with over more than 5,477,405 deaths worldwide as of 24 January 5, 2022. Clinically SARS-CoV-2 can manifest as disorders of cardiovascular, GI, neurological, and pulmonary systems. However, the most concerning complication of the virus is an acute hypercapnic respiratory failure requiring non-invasive positive pressure ventilation like BiPAP and in more severe cases invasive mechanical ventilation [1]. Sometimes acute hypoxemia can lead to a very severe acute lung injury and manifest as acute respiratory distress syndrome (ARDS). ARDS continues to be a major cause of mortality in intensive care units. Although mechanical ventilation with low Tidal Volume, early neuromuscular blockage, and prone positioning have shown to reduce mortality in ARDS, there is no specific treatment available [2]. Pathophysiology of ARDS involves diffuse alveolar damage due to the formation of hyaline membranes, increased capillary permeability, interstitial edema, and an influx of circulating inflammatory cells. Although wide evidence of research has shown the role of neutrophil influx and its activation within the lungs as important factors in the pathogenesis of ARDS, alveolar macrophages (AMs) and alveolar and bronchial epithelial cells are also involved [3,4]. Studies have shown that AMs play a role in modulation of the inflammatory responses and resultant lung injury [3,4]. AMs secrete pro-inflammatory cytokines, including TNF-alpha, IL-1 beta, and IL-6 which in turn stimulate neutrophils. Activated neutrophils release oxidants, proteases, leukotrienes, and platelet-activating factors resulting in the development of ARDS.

Flavonoid-Quercetin

Flavonoids are antioxidants. They scavenge particles in the body called free radical which are known to damage cell membranes, damage DNA, and cause cell death. Quercetin is one of the most abundant dietary flavonoids and is found in a broad range of fruits, vegetables, seeds, nuts, flowers, barks, broccoli, olive oil, green tea, red grapes, red wine, dark cherries, and berries like blueberries and cranberries. The highest concentration of flavonoids is found in vegetables like onion and broccoli, fruits like apples, cherries, and berries, and drinks like tea and red wine [5]. It is known to have antiviral, anti-inflammatory, cytotoxic, antimicrobial, and antioxidant effects. Studies have shown that regular diet provides small amounts of quercetin (< 1uM) which is not sufficient to exhibit chemo-preventative and/or protective effects on various organ systems like the cardiovascular system. However, the levels can be increased to appropriate plasma levels (> 10uM)

***Corresponding author:** Anand Seth, SK Patent Associates LLC, Dublin, Ohio, USA

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by appropriate quercetin enriched foods or supplements [6]. Quercetin suppresses H_2O_2-induced apoptotic events, including hypodiploid cells, activation of Caspase 3 enzyme activity, and lactate dehydrogenase release [2]. *In vitro* studies have shown that Quercetin plays a role in protecting against allergies, hay fever, heart disease, high cholesterol, HTN, interstitial cystitis, prostatitis, RA, and cancer.

Quercetin and COVID-19

COVID-19 is a highly infectious virus and can lead to comorbidities especially ARDS. The onset of COVID-19 related ARDS is typically 8-12 days, which is inconsistent with ARDS Berlin criteria, which defined a 1-week onset limit [7]. Studies have shown that quercetin plays a role in diminishing an acute lung injury, nitric oxide (NO), and malondialdehyde (MDA), and increases the antioxidant enzyme levels [8]. Animal sepsis models using cecal ligation and puncture have shown that single-dose of quercetin diminishes levels of YKL-40 (an inflammatory glycoprotein involved in endothelial dysfunction), and oxidant molecules (oxidase (XO)) [3]. Takashima, et al. [9] have shown that quercetin exhibits a prophylactic effect on lipopolysaccharide (LPS)-induced acute lung injury (ALI) in mice [9]. Lipopolysaccharides are present in the membrane of gram-negative bacteria and is considered as one of the major risk factors for ARDS. The same study also showed that intrathecal administration is a desirable method to effectively exert the cytoprotective effects of quercetin. Hayashi, et al. [10] showed that quercetin increases the levels of heme oxygenase (HO-1) expression and protects against hydrogen peroxide (H_2O_2)-induced cytotoxicity in lung epithelial cell lines [10]. Peroxide induced cytotoxicity is one of the etiologies of acute lung injury and in very severe forms can lead to ARDS. HO-1 plays an important role in defense against oxidant-induced lung injury during ARDS. Studies have shown increased HO-1 expression in lung tissues and bronchoalveolar lavage (BAL) fluid from patients with ARDS as body's compensatory role to fight against cytotoxicity. Several studies on various murine models of lung injury have also shown a protective role for HO-1.

Researchers have elucidated numerous antiviral properties of flavonoids. Molecular docking studies have shown that bioactive compounds found in medicinal plants like naringenin, quercetin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate appeared to have the best potential to act as COVID-19 main protease (M_{pro}) inhibitors as demonstrated by the binding energies [11]. This was also supported by a very recent study using in silico molecular dynamics docking studies by Peterson, et al [12]. In another docking study, it was shown that SARS-CoV2 has a favorable binding affinity for the human ACE2 receptor, which facilitates infection and molecules like quercetin can serve as a reasonable target to disrupt the viral S-protein -ACE2 interface [13]. The study by Meng, et al. [14] showed that quercetin improved arterial blood gas, lung water content, protein content, and cell counts in BAL in a dose-dependent manner [9]. It also decreased the expression of the intercellular adhesion molecule (ICAM-1) and macrophage inflammatory protein (MIP-2) as compared to the control groups. Soluble intercellular cell adhesion molecule -1 (sICAM-1) levels are significantly higher in both the pulmonary edema fluid and plasma from patients with ALI/ARDS [2].

Conclusion

Therefore, numerous studies have elucidated that quercetin holds strong therapeutic potential in suppressing the inflammatory cascade in acute lung injury and ARDS. Bioflavonoids, in general, and in particular quercetin hold a strong potential to be used in synergistic forms along with antivirals. The effective synergism of flavonoids with antivirals could potentially serve as a potent prophylactic supplement for the vaccinated and unvaccinated populations.

Competing Interests

The authors declare no competing interests.

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