Quercetin in Coronavirus Infections

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The COVID-19 outbreak seems to be the most dangerous challenge of the third millennium due to its highly contagious nature. Amongst natural molecules for COVID-19 treatment, the flavonoid molecule quercetin (QR) is currently considered one of the most promising. QR is an active agent against SARS and MERS due to its antimicrobial, antiviral, anti-inflammatory, antioxidant, and some other beneficial effects. QR may hold therapeutic potential against SARS-CoV-2 due to its inhibitory effects on several stages of the viral life cycle.

quercetin coronavirus COVID-19 infection

1. Introduction

Coronaviruses are positive-sense RNA viruses belonging to the family Coronaviridae and fall under the Nidovirales order. Since the beginning of the 21st century, coronaviruses have caused some of the most lethal outbreaks across the globe. For example, the SARS outbreak of 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks were caused by coronaviruses with a lethality rate of 10% and 37%, respectively [1]. A new member of the coronavirus family, SARS-CoV-2, is responsible for COVID-19, a highly contagious disorder that affects the respiratory system and leads to death in severe cases. Although the death rate of COVID-19 is much lower (~3.4%) than those of SARS and MERS, the highly contagious global outbreak has made COVID-19 one of the most lethal infections. The disease was first reported in Wuhan, China, in December 2019 and spread rapidly worldwide within months. COVID-19 has been declared a global pandemic by the WHO, and the number of coronavirus cases and the number of deaths continue to rise inexorably with a series of contagion waves [2][3][4]. Individuals infected with SARS-CoV-2 show pneumonia-like symptoms and develop a dry cough, intense fever, lung damage and inflammation, and breathing difficulty. In severe cases, lung damage is extensive and irreversible, leading to death. SARS-CoV-2 is a member of the β-coronavirus family and shares 79.5% sequence homology with the SARS-CoV virus (responsible for the SARS outbreak). SARS-CoV-2 also shares 96% sequence homology with bat SARS coronavirus, indicating that the novel coronavirus may have originated in bats. Once SARS-CoV-2 enters the body, the spike proteins of the virus interact with angiotensin-converting enzyme 2 (ACE2) receptors of the human alveolar epithelial cells. This interaction facilitates the entry of the virus into the host cells [5]. Studies have shown that SARS-CoV-2 is more lethal in patients with previous chronic disorders, such as diabetes, cardiovascular disorders, and lung diseases [5]. The current median incubation period of SARS-CoV-2 is 5.2 days (range: 0–24 days), and the median time between the symptoms and death is 14 days [5]. Despite the severity of the disease, no cure for COVID-19 is available. Some coronavirus proteins are

essential to viral entry and replication; among them, the most attractive targets for drug development are papain-like protease (PLpro), 3C-like protease (3CLpro), and spike protein (S) [6].

2. Quercetin Sources and Properties

The increasing interest in recent years in naturally occurring plant phytochemicals for the healing of various diseases is because they are generally less expensive and have fewer side effects than synthetic drugs. QR and several other natural polyphenols act as antioxidants, scavengers of ROS and other free radicals, and induce phase II detoxification enzymes [7][8]. QR is a hydrophobic citron-yellow crystal and plant-derived substance that has been subject to experimental validation to evaluate its characteristics and biological properties [9]. QR is one of the most ubiquitous flavonoid molecules. The characteristic feature of QR is the presence of five hydroxyl groups at positions 3, 5, 7, 3′, and 4′ with the electron-donating activity (**Figure 1**).

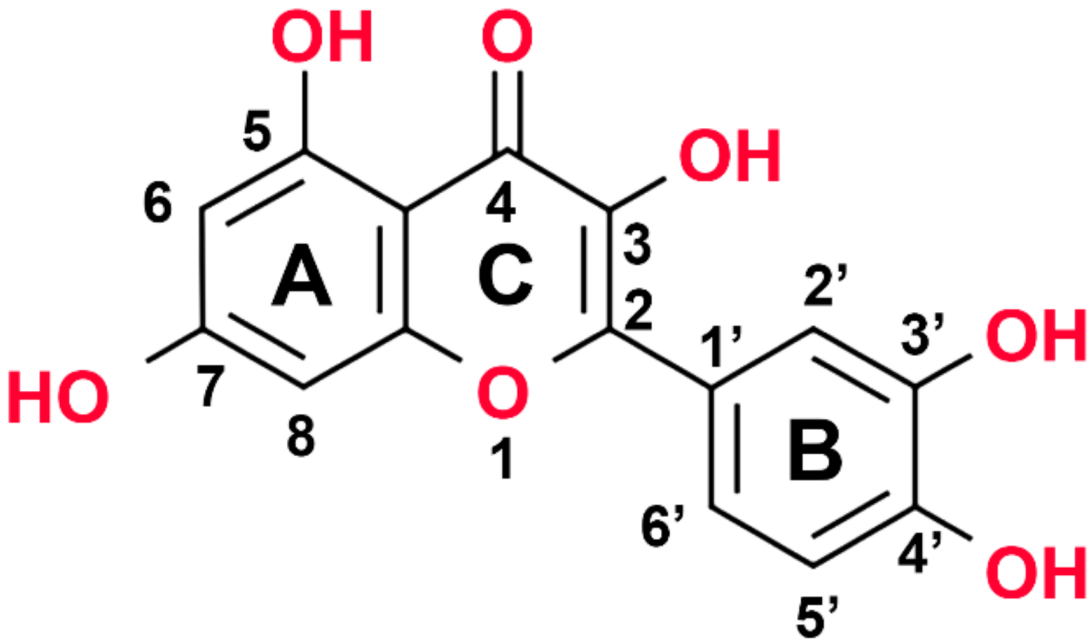

Figure 1. The structural formula of quercetin.

QR possesses several biological effects, including antioxidant, anti-inflammatory, antiviral, anticarcinogenic, cardioprotective, psychostimulant, and neuroprotective properties [9].

Its ability to inhibit free radicals, the cause of oxidative stress, can decrease the risk of metabolic disorders, cardiovascular diseases, and certain types of cancer [8][10].

Some common food ingredients rich in QR are apples, berries, grapes, citrus fruits, tea, many seeds, nuts, honey, propolis, and medicinal plants [11][12][13][14]. High QR content was evaluated in some commonly eaten vegetables in Japan. During the acquisition period in the summer of 2013, it was found that the content of QR was 30.6 mg/100 g in red leaf lettuce (*Lactuca sativa* L. var. *crispa*), 23.6 mg/100 g in asparagus (*Asparagus officinalis* L.), 12.0

mg/100 g in romaine lettuce (*Lactuca sativa* L. var. *longifolia*), 11.0 mg/100 g in onion (*Allium cepa* L.), and 9.9 mg/100 g in green pepper (*Capsicum annuum* L.), and 2.1 mg/100 mL of QR in green tea infusion [15]. QR was the most abundant phenolic compound in acacia honey samples, ranging from 123.5 to 240.2 µg/100 g of honey [16].

This flavonol is widely distributed in plants, primarily as water-soluble QR glycosides [12]. The QR and derivatives are stable in the stomach of the human body under the gastric acid influence; glucosides are hydrolyzed in the small intestine by brush border enzymes, such as lactase phlorizin hydrolase, beta-glucosidase enzyme to the aglycone form, and then absorbed [17][18]. Thus, before absorption into the enterocyte, sugars must be removed from the molecule [18].

3. Antioxidant, Anti-Inflammatory, and Antitumor Activities of Quercetin

Various research groups have reported the pharmacological properties of QR, such as antioxidant, anti-inflammatory, and antitumor properties. Due to these properties, QR is recommended for managing various disorders where oxidative stress, inflammation, and abnormal cell proliferation are major underlying causes. Zhang et al. observed that QR has a higher reduction potential than curcumin, comparable to the standard antioxidant Trolox. Moreover, QR reduced lipopolysaccharide (LPS)-induced production of reactive oxygen species and nitric oxide levels. The data indicated that QR is a powerful antioxidant and anti-inflammatory agent [14][19]. QR also increased the oxidative stress-fighting ability of the cells by stimulating the synthesis and expression of antioxidant enzymes, such as catalase, glutathione peroxidase, and superoxide dismutase. These enzymes' QR-induced expression protects the tissues from oxidative damage and injury [20]. Oxidative stress and inflammation are interlinked in the way that the presence of one of these phenomena induces the appearance of the other, and both are commonly observed in several chronic disorders, such as obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disorders (CVDs) [21]. This indicates that reducing oxidative stress/inflammation profoundly alleviates the symptoms of chronic diseases, and consequently, QR can be used as a powerful therapeutic strategy to treat these chronic disorders [21]. QR inhibits inflammation by reducing the expression of the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. The inhibition of these enzymes by QR reduces the synthesis of leukotrienes and prostaglandins, critical mediators of inflammation in the body [22][23]. Another key marker of inflammation in the body is C-reactive protein (CRP), and elevated levels of CRP have been implicated in several disorders, such as obesity, T2DM, and CVDs. QR inhibits the levels of several proinflammatory molecules, such as nitric oxide, COX, and CRP in hepatocyte cell lines [24].

Moreover, in [25], a dose of 80 mg significantly reduced chronic inflammation and helped in cases of adjuvant-induced arthritis. QR is also a potent anticancer agent by promoting apoptosis in cancer cells (CT-26, LNCaP, MOLT-4, and Raji cell lines) and reducing the volume of tumors [26]. QR inhibits cancer cell proliferation, reduces neovascularization of tumors, induces apoptosis, and prevents tumor metastasis [27]. QR (100 µM) causes cell growth inhibition and halts the proliferation of human T leukemic lymphoblasts (Jurkat) [28].

Considering its potent antioxidant properties, QR is actively investigated as a promising substance for the prevention and treatment of CVDs [29]. QR contributes to a decreased incidence of stroke due to radioprotective characteristics mediated by its impact on proteasomal proteolysis, as demonstrated in an experimental model of cholesterol-induced atherosclerosis in rabbits. One-month administration of QR decreased atherosclerotic lesion areas in the aorta [29]. In the same animal model, the QR derivative corvitin suppressed lipid peroxidation [30]. QR exhibited an antioxidant effect and a positive impact on endothelial function in patients with acute coronary syndrome with ST-segment elevation [31]. Treatment with QR-containing medicines positively affected hemodynamics and decreased about threefold the cardiac fibrosis area [32]. The anti-ischemic activity of intravenous QR in patients with ST-segment elevation myocardial infarction has been demonstrated [33].

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