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Mini Review

Anti-Inflammatory Activity of Flavonoids: Potential Role against COVID-19

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Abstract

The Coronavirus Disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has spread all over the globe and emerged as one of the most threatening transmissible disease. The infection can cause an acute respiratory distress syndrome associated with a systemic immune response and inflammation. Up to now, there is no specific drugs available for its treatment. Flavonoids are important natural polyphenolic compounds widely distributed in the plant kingdom. It has been demonstrated the potential role of these metabolites in the modulation of signaling pathways particularly those related to inflammation and immunity. This review focuses on the anti-inflammatory activity of flavonoids and their effectiveness as possible therapeutic options to fight SARS-COV-2 infection.

Keywords: Flavonoids; Anti-inflammatory; COVID-19; SARS-CoV-2

Introduction

Corona Virus Disease 2019 (COVID-19), triggered by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has rapidly spread all over the globe causing a worldwide pandemic. The infection can cause an acute respiratory distress syndrome associated with a systemic immune response and inflammation, affecting multiple organs that frequently can lead to a fatal event [1,2]. Elevated levels of cytokines and inflammatory markers Including Interleukins (IL) IL-6, IL-10, IL-1β, Granulocyte Colony-Stimulating Factor (GCSF), Interferon-Gamma (IFN-γ) Induced Protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1-α, and tumor necrosis factor-alpha (TNF-α) have been observed in severely ill COVID-19 patients. SARS-CoV-2 mainly increases IL-6, which has been recognized as one of the most important markers of unfavorable outcomes [3,4].

Currently, therapeutic options focus on antiviral agents as well as those that lead to the decrease in the inflammatory responses [5]. In this sense, natural products may play an important role in supportive and prophylaxis treatments [6].

Flavonoids are an important class of plant secondary metabolites widely distributed in the plant kingdom. They are important constituents of the human diet, mainly present in leafy vegetables, fruits, grains, tea, and red wine [7]. With an estimated 10,000 structures identified [8], these compounds are known to have antioxidant, anti-inflammatory, antibacterial, antiviral and antiproliferative properties along with safe preclinical and clinical profiles [9]. In this sense, the antiinflammatory and immune-modulating properties of flavonoids can be highly beneficial in the host immune response to viral infections alleviating infection-related symptoms, such as downregulating overwhelming inflammatory responses [6].

The aim of this review is specifically focused on the antiinflammatory activity of flavonoids and their effectiveness as possible leads to fight SARS-COV-2 infection. The information was collected by searching PubMed for articles published in 2020 up to June 5 2021 and was performed using the keywords "flavonoids and antiinflammatory and COVID-19" and was only limited to articles in the English language.

Flavonoids and COVID-19

In recent years, there has been an increasing progress in the elucidation of the mechanisms by which flavonoids exert their biological activities. It has been demonstrated that they exert beneficial effects through the interaction with cellular signaling pathways that mediate cell function under both normal and pathological conditions [10]. Flavonoids can block the expression and activation of many cellular regulatory proteins such as cytokines and transcription factors. The flavonol quercetin is the major polyphenolic flavonoid found in various vegetables and fruits. It has been approved by the US. Food and Drug Administration (FDA) because of its beneficial therapeutic properties. Quercetin exerts both anti-inflammatory (quercetin dose-dependently decreases the mRNA and protein levels of Intercellular Adhesion Molecule 1 (ICAM-1), IL-6, IL-8, MCP-1) and thrombin inhibitory actions [11]. The dual effect of quercetin in relation to acute kidney injury and its nephroprotective potential to SARS-CoV-2 patients has been discussed by Diniz et al. (2020) [12]. Pawar and Pal (2020) [13] proposed quercetin's use as adjunct therapy along with dexamethasone in severely ill COVID-19 patients and evaluate if quercetin can augment the therapeutic effect of dexamethasone in dexamethasone nonresponsive COVID-19 patients. Some important results have been reported for traditional herbal medicines rich in quercetin, and kaempferol. Network-based studies have identified these flavonols as "hub" components being employed in human respiratory viral infections, including SARS-CoV-2. Is predicted that they exert the pharmacological activity by synergistically intervening in key pathways that are implicated in both viral replication and virus-induced inflammation, chemokine production, vascular permeability, and oxidative stress-induced apoptosis [14].

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According to Mouffouk et al. (2021) [15], quercetin-3-O-glucuronide exerted anti-inflammatory effect by the suppression of c-Jun N-terminal Kinase (JNK) and Extracellular signal-Regulated Kinases (ERK) signaling pathways. Isorhamnetin (3-methylquercetin) contributes to the inhibition of acute inflammatory response by the inhibition of JNK and AKT/IKKα/β pathways activation which leads to nuclear factor kappa B (NF-κB) inactivation. Isorhamnetin-3-O-glucosylrhamnosyl-rhamnoside and isorhamnetin-3-O-glucosyl-rhamnoside exhibit significant antiinflammatory effects by several mechanisms of action including the regulation of cytokines secretion, the suppression of cellular infiltration, and the inhibition of Nitric Oxide (NO) production and Cyclooxygenase 2 (COX-2) activity.

Myricetin is a polyhydroxyflavonol commonly found in berries, fruits, vegetables, honey, red wine and tea. It regulates the expression of Mitogen-Activated Protein Kinase (MAPK), Signal Transducer and Activator of Transcription-3 (STAT-3), Toll-Like Receptors (TLR), NF-κB, Nuclear Factor Erythroid-2-Related Factor/Heme Oxygenase 1 (Nrf2/HO-1) pathway, among others. It enhances the immunomodulatory functions, suppresses cytokine storms, improves cardiac dysfunction and possesses antiviral potential [16].

Niu et al. (2021) [17] investigated the mechanisms of action of quercetin, luteolin, and rutin through IL-6 integrating network pharmacological approaches. The results obtained indicated that these compounds could decrease IL-6 expression, showing an anti-cytokine release syndrome effect in COVID-19 patients. A clinical trial, conducted in Turkey, aims to determine if the daily use of two 500 mg tablets of quercetin can prevent or treat the high-risk form of COVID-19. The results of this trial is complete but not yet published [18].

Rhamnocitrin (3,4',5-trihydroxy-7-methoxyflavone) has been identified as a potent inhibitor of endothelial activation, a pivotal cause of excessive cytokine production, leading to cytokine storm and severe pathology in infectious diseases such as COVID-19 pneumonia disease [19]. The flavone luteolin possesses anti-inflammatory activity by suppressing cytokine stormassociated elevated inflammatory response and inflammatory mediator release. Luteolin has neuroprotective properties, and these can provide beneficial effects in COVID-19 patients [20]. It has been demonstrated that this flavone inhibited IL-1β-induced inflammation in rat chondrocytes [21]. Luteolin is a potent inhibitor of mast cell release of histamine and a potent inhibitor of proinflammatory cytokine and chemokine release from mast cells. These cells could contribute to the pathogenesis of COVID-19 and any postinfectious inflammatory syndromes. To increase oral absorption, luteolin is used in its liposomal form in olive pomace oil [22]. The flavone apigenin reduced plasma levels of IL-6, TNF-α and IFN-γ *in vivo* [23] and apigetrin (apigenin 7-glucoside) reduced inflammatory factors including IL-lβ, TNF-α, IL-6, and Vascular Endothelial Growth Factor (VEGF) in mice [24].

Hesperidin is a flavanone glycoside mainly found in citrus fruits such as lemons and sweet oranges. Hesperidin inhibited the secretion of pro-inflammatory cytokines such as IFN-γ and IL-2 and IL-1β-stimulated inflammatory responses by inhibiting the activation of the NF-κB signaling cascade. Co-administrated with diosmin and heparin protect against venous thromboembolism which may prevent disease progression [25]. Hesperidin also triggered antiinflammatory responses resulting in a decreased level of IL-33 and TNF-α in mice co-treated with hesperidin and lipopolysaccharides [26]. According to Meng et al. (2020) [27], hesperidin ameliorated altered level of inflammatory mediators in ischemia/reperfusion-induced kidney injury in rats.

Naringenin is the aglycone of naringin, the bitter component of citrus fruits. This flavanone can downregulate the expression of several inflammatory markers such as TLR4, TNF-α, IL-1β, IL6, inducible Nitric Oxide Synthase (iNOS), and COX-2 through the attenuation of the NF-κB pathway and the activation of the AMP Activated Protein Kinase (AMPK). Alberca et al. (2020) [28] highlighted the mechanism by which naringenin may present an important anti-inflammatory role in COVID-19. Other authors discussed the promising effects and possible mechanisms of action of this compound against COVID-19 by attenuating inflammatory responses [5]. Epigallocatechin 3-Gallate (EGCG) is the most abundant ingredient in green tea leaves. Menegazzi et al. (2020) [1] analyzed the efficacy of EGCG in counteracting autoimmune diseases which are dominated by a massive cytokines production. EGCG inhibits STAT-1/3 and NF-κB transcription factors, whose activities are crucial in a multiplicity of downstream proinflammatory signaling pathways.

Caflanone (a cannabis flavonoid) inhibit the production of the cytokines IL-1β, IL-6, IL-8, macrophage inflammatory protein (Mip-1α) and TNF-α [29].

Phytochemical formulations and Traditional Herbal Medicines (THM) are employed as an adjunct strategy to antiviral drugs. In China, greater than 85% of SARS-CoV-2 infected patients are receiving THM in the treatment of COVID-19 [14,30].

Qing-Fei-Pai-Du (*QFPD*) is a Traditional Chinese Medicine (TCM) used in China to contain COVID-19. The decoction of QFPD exhibit immune regulation, anti-infection, antiinflammation, and multi-organ protection. The flavonoids baicalin, hesperidin, and hyperoside were identified as key molecules related to QFPD's effects. These include the inhibition of IL6, the Chemokine Ligand 2 (CCL2), TNF-α, NF-κB, the up-regulation of IL10 expression, and repressing platelet aggregation [31,32].

Maxingyigan (MXYG) decoction is a TCM prescription. The mechanism of action of MXYG against COVID-19 was studied by network analyses and virtual molecular docking. IL-6, caspase3 and IL-4 and the flavonoids quercetin, formononetin and luteolin were recognized as "hub" gene targets and key compounds, respectively. MXYG could prevent and treat COVID-19 based on its anti-inflammatory and immunity-based activities which include the activation of T cells, lymphocytes, and leukocytes, cytokine-cytokine-receptor interaction, and chemokine signaling pathways [33].

Dayuanyin (DYY) is a TCM classic prescription. DYY might play a vital role in treating COVID-19 by suppressing the inflammatory storm and regulating immune function. Molecular docking results showed affinity between the core compounds of DYY (kaempferol, quercetin, 7-methoxy2-methyl isoflavone, naringenin, formononetin) and core target genes such as IL-6, IL1β, and CCL2 [34].

Huang et al. (2020) [35] investigated the mechanism of action of *Toujie Quwen granule (TJQW)* in COVID-19, by an integrated network pharmacology approach. This TCM has proven to be

effective in the treatment of mild COVID-19 cases associated with the mechanisms that elevate immunity, suppress inflammatory stress, and regulate inflammatory responses. The flavonoids quercetin, kaempferol, luteolin, and oroxylin A were identified as key active compounds.

The species *Scutellaria baicalensis* (*SB*) has been widely used for thousands of years in TCM to treat cold, flu, fever and other diseases. Its major compounds are flavonoids such as baicalin, baicalein, oroxylin A, wogonin and norwogonin. SB exert an anti-inflammatory effect mainly by inhibiting the release of inflammatory factors and the expression of inflammatory related proteins. Thus, it is speculated that the therapeutic effect of SB on COVID-19 mainly focus on the inhibition of pro-inflammatory cytokine production and cut of cytokine storm, regulating immune response [36].

Pycnogenol® is an extract from the bark of *Pinus* species originating from France. It contains mainly procyanidins and their monomers (catechin and epicatechin). It has demonstrated antiinflammatory, vascular, and endothelium-protective effects in over 90 human clinical studies. **Pycnogenol**® may be beneficial for patients infected with SARS-CoV2 in supporting recovery and mitigating symptoms and longterm consequences [2].

Conclusions

Over the past 10-15 years, hundreds of research have been published regarding the potential of flavonoids as new therapeutic drugs to treat inflammatory disorders. As shown herein, the anti-inflammatory activity of flavonoids involves modulation of pro-inflammatory mediators through different intracellular pathways displaying a multitarget anti-inflammatory actions. As there is no known yet an effective treatment for patients with COVID-19, flavonoids appear as a promising group of natural compounds that can promote or overcome the SARS-CoV-2 infection due to the modulation of inflammatory processes and immune responses. However, most of the studies are *in vitro* assays or animal models. To date, human studies are scarce, therefore, further well-designed *in vivo* experiments, along with good quality clinical studies, are needed to obtain conclusive results. The most challenging factor is the flavonoids' low water solubility, which leads to lower absorption and consequently lower bioavailability after oral administration. In this sense, new technologies (microcapsules, nanoparticles, liposomes, inclusion complex, micelles, solid dispersión) [37] can be developed to improve flavonoid bioavailability by means of protective delivery systems to significantly improved water solubility, dissolution, absorption, or thermal stability.

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