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A Brief Review on Covid-19 and Flavonoids Antiviral Effects

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ABSTRACT

Coronavirus-related disease 2019 (COVID-19) became a pandemic in February 2020 and caused unprecedented health challenges. All around the globes researchers try to tackle the disease with existing treatments and known antiviral drugs of all kinds, or to develop novel compounds inhibiting viral spreading. Nature has provided us with immense supply of natural products with therapeutic characteristics. Flavonoids, already investigated as antivirals in general, are considered to have activities specific for the viral agent causing COVID-19, SARS-CoV-2. Anti covid-19 activity of Flavonoids can be categorized based on which part of viral cycle they affect.

Here in this mini-review we discussed the five major antiviral pathway which flavonoids have demonstrated the most effectiveness and can actually pave the way of managing this highly contagious novel disease and the major international concerns by developing new pharmacological agents by worldwide researchers.

INTRODUCTION

Flavonoids are widely used as phytomedicines. flavonoid phytomedicines with potential for development into prophylactics or therapeutics against coronavirus disease 2019 (COVID-19) have been reported. These flavonoid-based phytomedicines include: caflanone, Equivir, hesperetin, myricetin, and Linebacker [1]. And so many others.

A newly diagnosed coronavirus in 2019 (COVID-19) has affected all human activities since its discovery. Flavonoids commonly found in the human diet have attracted a lot of attention due to their remarkable biological activities. Flavonoids act via direct antiviral properties. and have shown antiviral activity via inhibition of viral protease, RNA polymerase, and mRNA, virus replication, and infectivity. Baicalin, quercetin and its derivatives, hesperidin, and catechins are the most studied flavonoids in this regard [2].

Following the COVID-19 pandemic, the interest of the potential therapeutic use of flavonoids against coronavirus infection focused

on SARS-CoV-2 virus. Among natural compounds, the flavonoids class constitutes a possible target for antiviral drugs due to its large spectrum of biological properties (antioxidant, anti-inflammatory, and antiviral activities. This class of secondary metabolites occurs abundantly in a variety of medicinal plants, fruits and vegetables. Indeed, onions, kale, lettuce, tomatoes, apples, grapes and berries are considered as rich sources of flavonoids. kaempferol, quercetin, myricetin, fisetin and their derivatives were the most documented molecules with antiviral activities against SARS-CoV-2 [3]. Flavonoids can exhibit potential inhibitory activity against SARS-CoV-2 by binding to essential viral targets required in virus entry and/ or replication. Flavonoids also showed excellent immunomodulatory and anti-inflammatory activities including the inhibition of various inflammatory cytokines [4].

For the management of COVID-19 infection, various molecular targets playing important role including host cell Receptor-Angiotensin-converting enzyme ACE2 and viral proteins such as S protein various cysteine proteases such as papain-like cysteine protease (PLpro) or Chymotrypsin like nprotease (3CLpro), and RNA-dependent RNA polymerase (RdRp)) could be evaluated [5].

Here The five important targets chosen to review the main protease (Mpro), Spike receptor binding domain (Spike-RBD), RNA - dependent RNA polymerase (RdRp or Nsp12), non-structural protein 15 (Nsp15) of SARS-CoV-2 and the host angiotensin converting enzyme-2 (ACE-2) spike-RBD binding domain [6].

SARS-Cov-2-Enzyme Inhibitory Effects

Coronaviruses generate three types of viral proteases, including 3-chymotrypsin-like cysteine (3CLpro), papain-like protease (PLpro), and main protease (M pro). 3CLpro is important for the SARS-CoV life cycle, PLpro plays a role in SARS-CoV-2 replication, and Mpro is responsible for the maturation of functional proteins in SARS-CoV-2. Quercetin and quercetin-β-galactoside downregulated PLpro, 3CLpro, deubiquitination, and DeISGylation activity in SARS-CoV kaempferol to 3CLpro and PLpro of SARS-CoV expressed in E. coli caused antiviral effects via inhibition of these enzymes [2].

SARS-CoV-2 main protease (M^{pro}) is the enzyme responsible for umpiring the replication and transcription of the virus), making it a target for inhibitors towards the design and development of new COVID-19 drugs (Anand et al. 2002) [7]. Both quercetin and kaempferol sulfates and glucuronides, described as promising SARS-CoV-2 3CLpro and RdRp inhibitors, could have a key role against these proteins, since the virus is also dominant in plasma. rutin, nicotiflorin, and their putative human metabolites, can play a key role as inhibitors of the SARS-CoV-2 3CLpro and RdRp. Such derivatives, which are expected in plasma, are in fact the most likely compounds for targeting these viral proteins, via oral intake of these flavonoid glycosides [8].

flavonoids such as herbacetin (10) (Docking Score –9.263), rhoifolin (11) (Docking Score —9.565), and pectolinarin (12) demonstrated anti-SARS-CoV $3CL^{pro}$ activity. Another flavonoid amentoflavone (13) (Docking Score −11.42) is the most effective flavonoid inhibiting SARS-CoV $3CL^{pro}$ [5].

Baicalin, a glucuronated flavone showed an effective inhibition (IC50 of ~ 35 μM). Two rutinosylated flavonoids, the flavone pectolinarin and the flavonol herbacetin also proved to prominently inhibit 3CLpro (IC_{50} of ~ 54 and 51.5 μM respectively) [9].

The promising compounds include five flavones orientin, baicalin, pectolinarin, homoplantaginin and rhoifolin and two flavonols; herbacetin, rutin. Among them, baicalin, herbacetin and pectolinarin revealed the prominent inhibitory activity against SARS-CoV-2 3CLpro [10].

flavonoid based phytochemicals of calendula (rutin, isorhamnetin-3-O-β-D, calendoflaside) may be highly effective for inhibiting M^{pro} which is the main protease for SARS-CoV-2 causing the deadly disease COVID-19 [11]. Herbacetin, rhoifolin and pectolinarin were the best inhibitory compounds against SARS-CoV 3CLpro in the flavonoid library [12].

Targeting the main protease (M^{pro}) of the causative agent, SARS-CoV-2 has great potential for drug discovery and drug repurposing efforts [13].

Anti-Spike Protein (S) of The SARS-Cov-2 Effects

Spike protein (S) of the SARS-CoV-2 plays a crucial role in entering viruses into the host cell by binding to Angiotensin-Converting Enzyme 2 (ACE-2), and this specific interaction represents a promising drug target for the identification of potential drugs. flavonoids (hesperidin, naringin, ECGC, and quercetin) showed excellent pharmacokinetics with proper absorption, solubility, permeability, distribution, metabolism, minimal toxicity, and excellent bioavailability. With Also strong binding affinity to RBD of nCoV-SP and ACE-2. These identified lead flavonoids may act as potential compounds for developing effective drugs against SARS-CoV-2 by potentially inhibiting virus entry into the host cell [14].

several extracts/derivatives from the herbs belonging to family polygonaceae have been reported to inhibit the SARS-CoV S protein interaction with Angiotensin-converting enzyme ACE2 receptor. Anthraquinone compound namely emodin (1), a plant extract isolated from genus *Polygonum,* and *Rheum* has efficiently impeded the interaction of S protein and Angiotensin-converting enzyme ACE2 receptor [5]. The flavone luteolin inhibited the attachment and entry of SARS-CoV virions into human Vero E6 cells, probably after binding to the S2 domain of the spike [9].

Both flavonols myricetin and linebacker indicated potential binding efficacy to the S protein, helicase and to many protease sites and had the ability to interact with the ACE2 receptor causing con-

formational changes and viral entry inhibition [15].

RNA - Dependent RNA Polymerase Inhibitory Effects

Another interesting field of investigation is represented by inhibition of RNA viral replication, proposing RdRp as a candidate for targeted drug development. To this purpose, a molecular screening evidenced that theaflavin can interfere with the catalytic pocket of SARS□CoV□2 RdRp. By means of molecular docking, it has been demonstrated that hydrophobic interactions are involved in binding of theaflavin to RdRp. In addition, hydrogen bonds were established between functional moieties of theaflavin and residues of RdRp [16].

Two network analyses on SARS-CoV-2 drug finding were performed. One is based on COVID-19 disease-related genes and drugs targeting these genes, where also two flavonoids, myricetin and quercetin, were revealed to be promising drugs. The other study used unsupervised learning, a machine-learning method, on gene expression profiles of SARS-CoV-2-infected vs non-infected cells), by which also quercetin was detected as a potential flavonoid drug against COVID-19 [9].

A recent investigation by Zandi et al. revealed the in vitro antiviral effect of baicalin and baicalein against SARS-CoV-2 infection in Vero CCL-81 cell line through inhibition of RdRp, with a higher potency by baicalein [4].

Effects on Non-Structural Protein 15 (Nsp15) of SARS-Cov-2

Virus replication takes place at the level of the cytoplasmic membrane and is mediated by a multi-subunit Replication/Transcription Complex (RTC) formed by different viral NSPs. RNA helicases (NSP13) represent the second most conserved subunit of the RNA synthesis machinery in (+) RNA coronaviruses and are involved in diverse steps of their life cycle.

natural compounds that inhibited the ATP hydrolysis activity of nsP13 flavonoids have been measured. Scutellarein have shown inhibition of ATPase activity of nsP13 by more than 90% while a few compounds such as myricitrin, amentoflavone, diosmetin-7-*O*-Glc-Xyl and taraxerol exhibited some degree of inhibition [17].

Effects on the Host Angiotensin Converting Enzyme-2 (ACE-2) Spike-RBD Binding Domain

Angiotensin-converting enzyme ACE2 receptor is a human receptor to the SARS and SARS-CoV-2. These receptors facilitate entry of three CoV strains (e.g. NL63, SARS-CoV, and SARS-CoV-2), which are present most abundantly in the lungs (predominantly in type 2 pneumocytes and macrophages), testis, brain, heart, blood vessels, and the kidney. Various natural compounds such as baicalin, scutellarin, nicotianamine and glycyrrhizin have been reported to have potential anti-2019-CoV effects by preventing the attachment and entry of virus. Particularly baicalin, extracted from plant Scutellaria baicalensis Georgi demonstrated an excellent antiviral and anti-SARS activity [5].

it is proven that the S protein of SARS-CoV-2 binds with 10−20-fold higher affinity to ACE2 than that of SARS-CoV Thus, inhibition of ACE2 via a competing substance, seems to be a reasonable approach for preventing SARS-CoV-2 infections. Quercetin had potent inhibitory effects on ACE in vitro, and in vivo when tested in rat models [18].

Two flavonoids were observed to have very good binding values to either the spike protein or ACE□2 in several studies, namely hesperidin and Epigallocatechin Gallate (EGCG) [9].

Bioactive compounds from flavonoid derivatives are valuable for the development of drugs. Other flavonoids including flavones and flavonoids were investigated for having antiviral potential, and many of them showed significant antiviral responses in both in vitro and in vivo studies. Naringenin and hesperetin (flavanon), hesperidin (flavanonone glycoside), baicalin and neohesperidin (flavone glycoside), nobiletin (*O*-methylation), scutellarin (flavone), nicotinamin (nonproteinogenic amino acids), and glycyrinodin are amongst natural ACE2 inhibitors [19- 21].

The application of flavonoid-based scaffolds in the design of new ACE2 inhibitors could be a good approach [22].

CONCLUSION

Based on the information put forth in this review, it can be concluded that Flavonoids could be a key feature to combat COVID-19 infection. In summary, we have discussed the target-specific antiviral potential of several Flavonoids family. The use of the flavonoids quercetin, herbacetin, and isobavachalcone in adjuvant therapy with other proposed antiviral drugs may present another interesting approach to impedes this Covid-19 pandemic. Further studies are needed to determine the best approach in using flavonoids as anti-COVID-19 drugs and overcoming its limitations such as the poor bioavailability of flavonoids.

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