Flavonoids are promising safe therapy against COVID-19

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Abstract Flavonoids are a class of phenolic natural products, well-identified in traditional and modern medicines in the treatment of several diseases including viral infection. Flavonoids showed potential inhibitory activity against coronaviruses including the current pandemic outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and designated as COVID-19. Here, we have collected all data related to the potential inhibitory mechanisms of flavonoids against SARS-CoV-2 infection and their significant immunomodulatory activities. The data were mapped and compared to elect major flavonoids with a promising role in the current pandemic. Further, we have linked the global existence of flavonoids in medicinal plants and their role in protection against COVID-19. Computational analysis predicted that 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. Further, flavonoids showed significant ability to reduce the exacerbation of COVID-19 in the case of obesity via promoting lipids metabolism. Moreover, flavonoids exhibit a high safety profile,

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suitable bioavailability, and no significant adverse effects. For instance, plants rich in flavonoids are globally distributed and can offer great protection from COVID-19. The data described in this study strongly highlighted that flavonoids particularly quercetin and luteolin can exhibit promising multi-target activity against SARS-CoV-2, which promote their use in the current and expected future outbreaks. Therefore, a regimen of flavonoid-rich plants can be recommended to supplement a sufficient amount of flavonoids for the protection and treatment from SARS-CoV-2 infection.

Keywords COVID-19 · SARS-CoV-2 · Flavonoids · Treatment · Immunomodulatory · Global distribution

Abbreviations

ACE2	Angiotensin converting enzyme II
ADME	Absorption, distribution, metabolism, and excretion of a drug molecule
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CCL5	Inflammatory chemokines
COVID-19	Coronavirus disease-2019
ΔG	Binding energy
DCs	Dendritic cells
E protein	Envelope protein
ERK	Extracellular-signal regulated kinase pathway
I.P.	Intraperitoneal
C_{50}	The concentration of drug required for 50% inhibition
IL-6	Interleukin-6
LPH	Lactase phloridzin hydrolase
LPS	Lipopolysacccharides
M protein	Membrane glycoprotein
MED	Mediterranean
MERSCoV	Middle East respiratory syndrome coronavirus
M^{pro}	Main protease
N protein	Nucleocapsid protein
NF-κB	Nuclear factor kappa B pathway
Nsps	Non-structural proteins
PDB	Protein data bank
PLpro	Papain-like protease
PD	Peptidase domain
RBD	Receptor binding domain
RdRp	RNA dependent RNA Polymerase
SARS-CoV-2	Severe acute respiratory syndrome
SGLT1	Intestinal Na +—dependent glucose co-transporter
Sprotein	Spike protein
TMPRSS2	Type 2 transmembrane serine protease
TNF-α	Tumor necrosis factor alpha
WHO	World Health Organization

Introduction

On December 2019, a novel coronavirus outbreak was reported as a severe acute respiratory disease syndrome coronavirus 2 (SARS-CoV-2) (Rabi et al. 2020; Yang and Shen 2020). Early on January 12, 2020, the World Health Organization (WHO) announced an unprecedented pandemic outbreak of new discovered virus from the betacoronavirus family that has not been previously identified in human and was named 2019 novel coronavirus or "2019 nCoV" (Chen et al. 2020b). Subsequently, on February 11, 2020, WHO announced the official name of the disease caused by 2019-nCoV as Coronavirus Disease 2019, which is abbreviated as COVID-19.

COVID-19 is the sixth CoV outbreak identified globally (WHO 2020). SARS-CoV-2 is closely related to SARS-CoV (Ge et al. 2013; Lau et al. 2005). In addition to COVID-19 outbreak, coronavirus has caused three zoonotic outbreaks within the last two decades that belong to betacoronavirus family (Boopathi et al. 2020). These include acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) in China during the 2001 to 2003 period and from 2012 to 2015 in Saudi Arabia (Boopathi et al. 2020). SARS-CoV-2 can develop severe complications including septic shock and multiple organ failure that may result in death especially in people at high risk including immunocompromised and those with underlying medical conditions such as cancers, diabetes, cardiovascular disease, and chronic respiratory diseases. The common disease symptoms of COVID-19 can include fever, cough, shortness of breath, and dyspnea, while in severe cases, SARS-CoV-2 infection can cause pneumonia, severe acute respiratory syndrome, organ failure, and death (Wang et al. 2020).
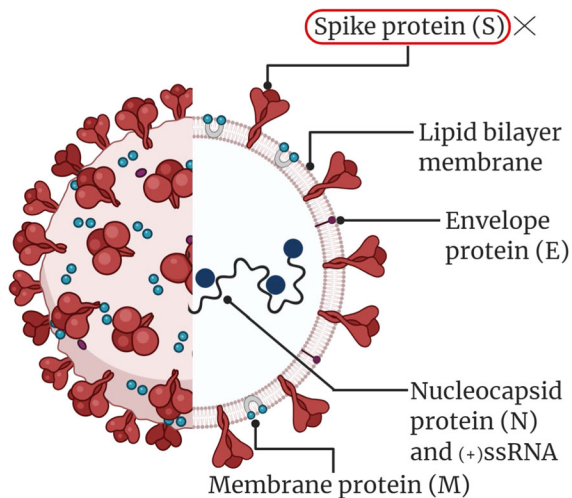
Fig. 1 Diagrammatic cartoon drawing of SARS-CoV-2 showing the main structural features of the virus. The red frame and cross sign indicated a critical therapeutic target

SARS-CoV-2 contains four essential proteins including membrane glycoprotein (M), spike (S) protein, envelope (E) protein and nucleocapsid (N) protein (Fig. 1) (Mahmoud et al. 2020). The first three proteins are embedded in a lipid bilayer, while the N protein coats the single-stranded positive-sense viral RNA (Jin et al. 2020). E protein plays a vital role in the virus assembly (Gupta et al. 2020), whereas M protein is the most abundant protein that is considered as a central organizer for coronavirus assembly (Boopathi et al. 2020). The N protein plays an important role in virus transcription and translation (Boopathi et al. 2020). There are several non-structural proteins (nsps) such as nsp12 for RNA-dependent-RNA polymerase (RdRp), nsp3 for papain-like protease (PLpro) and nsp5 for the viral main protease (M^{pro}) (Dai et al. 2020). The S protein is located on the surface of the virus (Dai et al. 2020) and facilitates the SARS-CoV-2 entry into the human cell by binding to the host cell surface receptor angiotensin converting enzyme-2 (ACE-2) (Kirchdoerfer et al. 2016; Simmons et al. 2013). The S protein is composed of two main functional domains, the N-terminal S1 and C-terminal S2 subunits (Beniac et al. 2006). The S1 contains receptor binding domain (RBD) that is necessary for the binding with the host cell receptors (Wong et al. 2004), and S2 mediates the membrane fusion (Walls et al. 2020). SARS-CoV-2 RBD has 10–20-fold higher

ACE-2 binding affinity than SARS-CoV RBD (Kirchdoerfer et al. 2018; Wrapp et al. 2020).

Coronavirus infective cycle can be summarized in Fig. 2 (Al-Horani et al. 2020). The S protein of the virus first binds to ACE-2 receptor (Astuti and Ysrafil 2020), which is proteolytically activated by cleavage with human type 2 transmembrane serine (TMPRSS2) (Russo et al. 2020) into two subunits, S1 and S2 (Astuti and Ysrafil 2020), which allows the virus entery (Yang and Shen 2020). Subsequently, the viral particle is uncoated to deliver the positive sense single-stranded RNA [(+)ssRNA] into the cytoplasm (Liu et al. 2020). RNA-dependent RNA polymerase (RdRp) is an essential enzyme required for viral replication and transcription (Oostra et al. 2007).

The outbreak due to SARS-CoV-2 infection creates devastating social, economic, political, and global health problems, while a number of vaccines and medications were either approved or in clinical studies (Wang et al. 2020). Recently, several vaccine platforms were entered into the clinical evaluation (Le et al. 2020). These include (i) Nucleic acid vaccines as mRNA-based-vaccines such as Moderna (Mahase 2020), BioNTech/Pfizer (Müller et al. 2021), CureVac/ Bayer (Rosales-Mendoza et al. 2020), and Inovio as DNA-based vaccines (Calina et al. 2020); (ii) Viral vector vaccines as Ad vector (ChAdOx1) developed by AstraZeneca (Wise 2021), Johnson – Johnson vaccine developed by Janssen Vaccines (Livingston et al. 2021) and Sputnik V (Jones and Roy 2021) developed by Gamaleya Research Institute of Epidemiology and Microbiology; (iii) Inactivated virus as Sinovac vaccine (Palacios et al. 2020) developed by China Sinovac biotech company; (iv) Antigen-based vaccine EpiVacCorona that was developed by the Vector Institute (Ryzhikov et al. 2021). On the other hand, the treatments suggested for COVID-19 are limited to those either still in clinical trials such as favipiravir (Pilkington et al. 2020), ribavirin (Khalili et al. 2020), lopinavir-ritonavir (Dalerba et al. 2020), emetine (Choy et al. 2020), hydroxychloroquine (Chen et al. 2020a), methionine (Zhang et al. 2020), homoharringtonine and ivermectin (Elgazzar et al. 2020) or initially approved by U.S. FDA such as remdesivir (Beigel et al. 2020). Furthermore, CR3022 monoclonal antibody with binding affinity to the RBD of SARS-CoV-2 S protein was suggested as a therapeutic approach (Lee et al. 2020). IFN-I with an established role in suppression
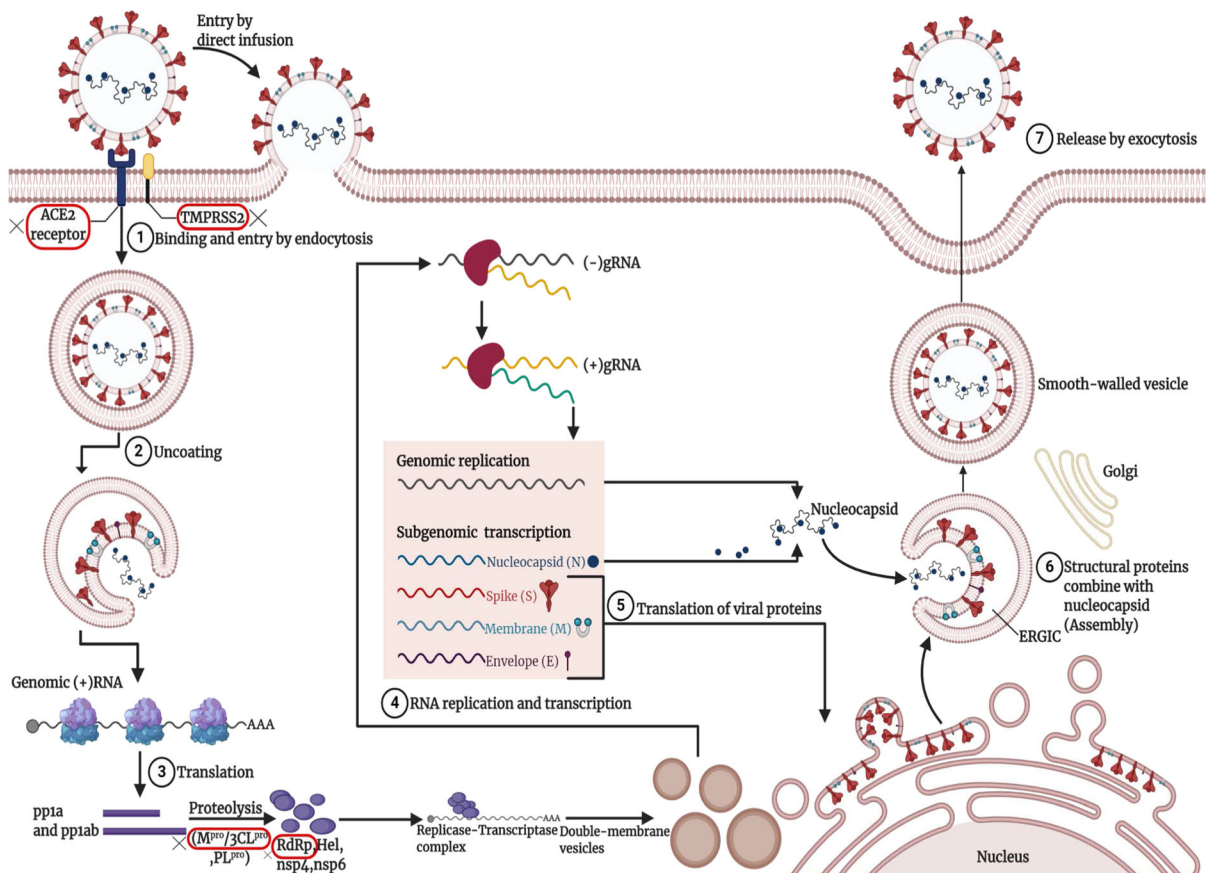
Fig. 2 Diagrammatic drawing of the virus life cycle and critical therapeutic targets indicated in red frame and cross sign
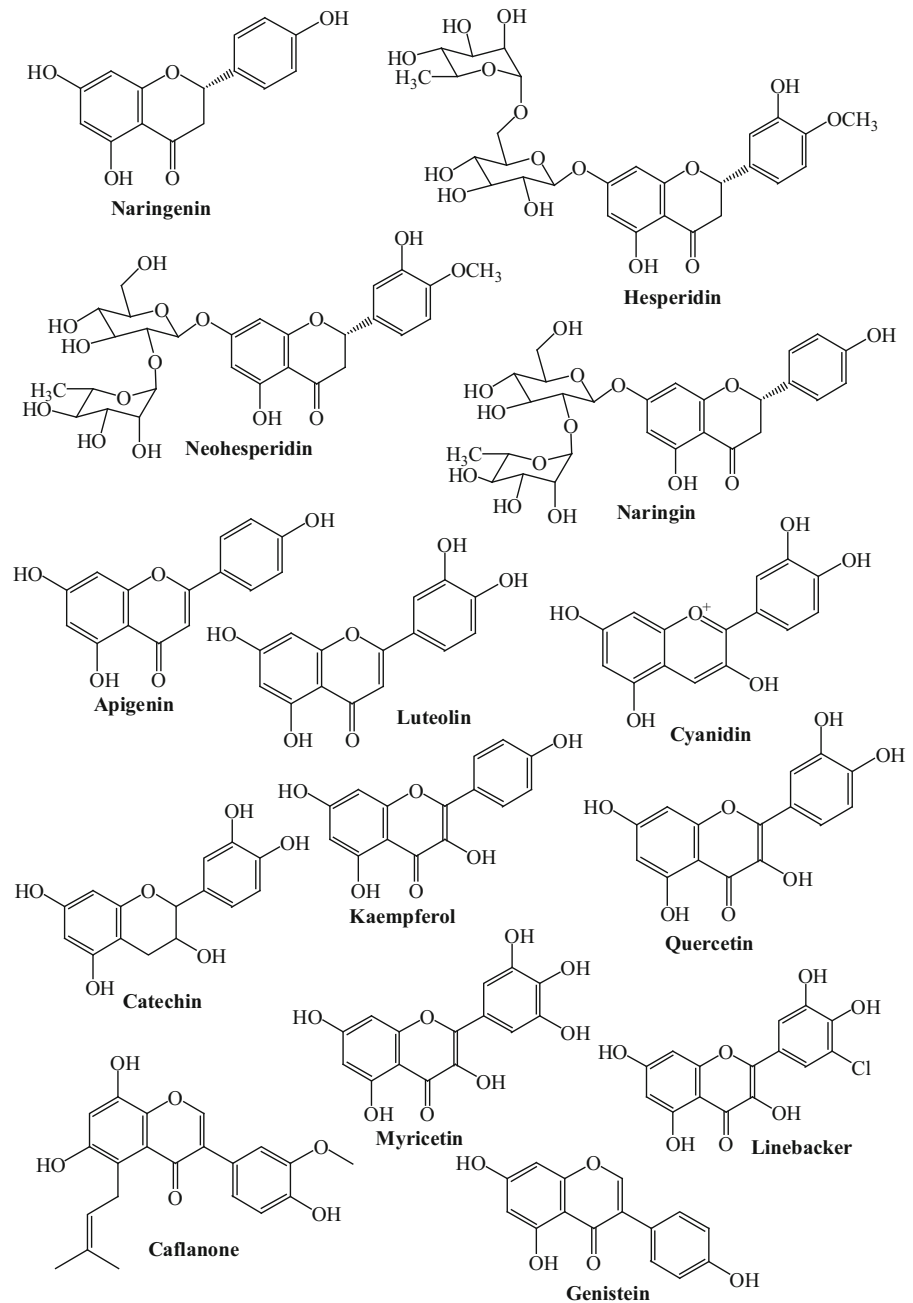
and treatment of SARS-CoV, MERS-CoV and SARS-CoV-2 infections was also suggested (Lee and Shin 2020).

Natural products can provide effective antiviral activity against SARS-CoV-2. For instance, flavonoids are phenolic phytochemicals (Solnier and Fladerer 2020) that show various important biological activities including antiviral, antioxidant, and anti-inflammatory activities (Krych and Gebicka 2013; Ragab et al. 2014; Tian et al. 2013; Zhang et al. 2015). Flavonoids are widely distributed in medicinal plants, vegetables, fruits, nuts, seeds, tea, honey, and propolis (Ahmad et al. 2015; Yahia 2019). This review highlights the importance of flavonoids as treatment and prophylaxis against SARS-CoV-2, their predicted therapeutic targets and proposed regimen supplements.

Flavonoids-mediated inhibition mechanisms of SARS-CoV-2: in silico study

All flavonoids identified in silico as potential inhibitors to SARS-CoV-2 are listed in Fig. 3 and Table 1. It has been identified that M^pro is necessarily required for the replication of SARS-CoV (Yang et al. 2003). Further analysis showed that M^pro of SARS-CoV-2 and SARS-CoV are very similar (Tahir Ul Qamar et al. 2020). Therefore, targeting M^pro is of great therapeutic value. A molecular docking study revealed that naringenin can bind to M^pro by forming H-bond with the amino acids of the M^pro active site, indicating the inhibition capability of naringenin to SARS-CoV-2 M^pro (Khaerunnisa et al. 2020). Recent studies showed that hesperidin has an inhibitory activity against SARS-CoV-2 by binding to SARS-CoV-2 M^pro, the receptor-binding domain of S protein (RBD-S) and the peptidase domain of ACE-2 (PD-ACE-2) (Adem et al. 2020; Tallei et al. 2020; Utomo et al. 2020). An in

silico study showed that quercetin has potential inhibitory activity against SARS-CoV-2 (Sekiou et al. 2020). Quercetin showed excellent binding affinity to M^pro (Sekiou et al. 2020). Another in silico study was performed to identify the inhibitory activity of some food bioactive flavonoids against SARS-CoV-2. The results showed that cyanidin and genistein have a comparable binding affinity to M^pro and RdRp compared to Nelfinavir and Lopinavir (Pendyala and Patras 2020). Furthermore, a computational study indicated the potential importance of several flavonoids including kaempferol, quercetin, luteolin-7-glucoside, apigenin-7-glucoside, naringenin, catechin, and epigallocatechin as potential inhibitors to SARS-CoV-2 M^pro (Khaerunnisa et al. 2020). Additionally, rutin was suggested as a potential anti-SARS-CoV-2

Table 1 Flavonoid classes identified in silico as potential inhibitors to SARS-CoV-2 targets

Flavonoid class and compound	SARS-CoV-2 target	Binding energy (ΔG)	References
Flavanones			
Naringenin	M^{pro}, ACE-2	− 7.89 (M^{pro}), − 6.05 (ACE − 2)	(Cheng et al. 2020; Khaerunnisa et al. 2020)
Hesperidin Neohesperidin	M^{pro}, ACE-2, RBD-S	− 8.3 (M^{pro}), − 9.50 (ACE − 2), − 10.4 (RBD − S)	(Adem et al. 2020; Ngwa et al. 2020; Tallei et al. 2020; Utomo et al. 2020)
Naringin	TMPRSS2	− 8.82	(Chikhale et al. 2020)
	TMPRSS2	− 7.57	(Chikhale et al. 2020)
Anthocyanidins			
Cyanidin	M^{pro}, RdRp	− 7.9 (M^{pro}), − 8.8 (RdRp)	(Pendyala and Patras 2020)
Flavanols			
Catechin	M^{pro}	− 7.24	(Khaerunnisa et al. 2020)
Epigallocatechin	M^{pro}	− 6.67	(Khaerunnisa et al. 2020)
Flavones			
Apigenin	M^{pro}	− 7.83	(Khaerunnisa et al. 2020)
Luteolin	M^{pro}, ACE-2, S	− 8.17 (M^{pro})	(Khaerunnisa et al. 2020)
Caflanone	ACE2	− 7.9	(Ngwa et al. 2020)
Isoflavones			
Genistein	M^{pro}, RdRp	− 7.6 (M^{pro}), − 8.6 (RdRp)	(Pendyala and Patras 2020)
Flavonols			
Quercetin	M^{pro}, TMPRSS2, ACE-2, S	− 8.47 (M^{pro}), − 6.90 (TMPRSS2)	(Chikhale et al. 2020; Khaerunnisa et al. 2020; Sekiou et al. 2020)
Kaempferol	M^{pro}, TMPRSS2	− 8.58	(Khaerunnisa et al. 2020)
Myricetin	ACE-2, TMPRSS2	− 8.9 (ACE − 2), − 4.83 (TMPRSS2)	(Chikhale et al. 2020; Ngwa et al. 2020)
Icariin	TMPRSS2	− 8.83	(Chikhale et al. 2020)
Linebacker	ACE-2	− 9.2	(Ngwa et al. 2020)

M^{pro} following a virtual screening of 2030 natural compounds (Xu et al. 2020).

A well-identified therapeutic strategy is by targeting the ACE-2 receptor. Due to the high similarities of the receptor-binding domain of S protein between SARS-CoV and SARS-CoV-2, both viruses showed excellent ability to bind to human ACE-2 receptor (Wan et al. 2020). Molecular docking studies were performed to investigate the binding affinity of several flavonoids to ACE-2 and/ or S protein. It has been shown that hesperetin, myricetin, linebacker and caflanone showed excellent binding affinity to S protein, helicase and ACE-2 receptor and hence can block the entry of the virus (Ngwa et al. 2020). Another study showed that naringenin has low binding energy to the ACE-2 receptor, indicating a high binding affinity to ACE-2 (Cheng et al. 2020). A

computational study revealed that baicalin flavonoid showed excellent binding affinity to S protein compared to abacavir and hydroxychloroquine. Baicalin was also reported with antiviral activity against other viral infections (Pandey et al. 2021).

Human TMPRSS2 is a critical protease used by the virus for its activation via S protein cleavage (Hoffmann et al. 2020). A computational study was performed and the results showed that neohesperidin, myricitrin, quercitrin, naringin, and icariin flavonoids have a strong binding affinity towards TMPRSS2 (Chikhale et al. 2020). A comprehensive computational study also indicated that silybin may have a high binding affinity to TMPRSS2 that is required for viral entry, and chrysin with outstanding binding affinity to the M^{pro} of SARS-CoV, MERS-CoV and SARS-CoV-

2. Chrysin also inhibited the interaction of ACE-2 with the S protein of SARS-CoV-2 (Jha et al. 2020).

Flavonoids-mediated inhibition mechanisms of SARS-CoV-2: in vitro study

Quercetin has displayed significant inhibition activity against SARS-CoV M[pro], expressed in *Pichia pastoris*, at IC$_{50}$ 73 μM (Nguyen et al. 2012). Quercetin showed anti-SARS-CoV-2 and immunomodulatory activities particularly when co-administered with vitamin C. Both exert synergistic effect and can be employed for prophylaxis in high-risk populations (Colunga Biancatelli et al. 2020). Similarly, herbacetin, rhoifolin and pectolinarin flavonoids can efficiently block the enzymatic activity of SARS-CoV M[pro] (Jo et al. 2020). Fractionation-based anti-papain protease activity of the methanolic extract of *Paulownia tomentosa* fruits identified different geranylated flavonoid derivatives as potent inhibitory activity to SARS-CoV papain protease (Báez-Santos et al. 2015).

The aforementioned data indicated that several flavonoids showed potential inhibition activity to SARS-CoV-2 by possible targeting of essential proteins in the viral life cycle. However, a limited number of flavonoids have been tested in vitro. Therefore, it is important to validate the computational study by performing an appropriate biological activity.

Immunomodulatory and anti-inflammatory activities of flavonoids

Severe cases of COVID-19 have been characterized by developing cytokine storm (Mahmudpour et al. 2020), a life-threatening complication associated with the acute respiratory distress syndrome (ARDS). Those cases may represent more than 33% of COVID-19 hospitalized patients and ∼ 40% mortality rates (Tzotzos et al. 2020). Comparative analysis of blood samples showed that severe COVID-19 patients have higher plasma levels of GCSF, IP10, MCP1, MIP1A, IL-2, IL-6, IL-7, IL-10 and TNF-α, indicative of high serum levels of pro-inflammatory cytokines (Cheng et al. 2020). Inhibition of hyperinflammatory response and regulation of immune responses is an important strategy to attenuate cytokine storm (Mahmudpour et al. 2020). Interestingly, flavonoids exhibit significant immunomodulatory and anti-inflammatory activities (Hodek et al. 2002; Hosseinzade et al. 2019), which can be employed as a possible treatment or amelioration of complicated COVID-19 symptoms. Below are the most important flavonoids classes that can be employed as immunomodulators (Table 2).

Flavanones: naringenin and hesperetin

Naringenin has been shown to exhibit promising immunomodulatory activity by reducing the severity of inflammatory responses (Tutunchi et al. 2020). A study that examined the effect of naringenin on rats' lungs, exposed to benzo[α]pyrene, showed that naringenin exerted a protective effect by reducing the pro-inflammatory cytokines through inhibition of NF-κB (Ali et al. 2017), which results in reducing the expression of COX-2 and restoring the normal histology of the rat lungs (Ali et al. 2017). Another study showed that the administration of naringenin can significantly reduce the expression of NF-κB, iNOS and TNF-α in rats' lungs with sepsis (Fouad et al. 2016). Besides, naringenin markedly reduced the inflammatory cytokine production, pulmonary oedema, IL-6 and MPO activity (Fouad et al. 2016). Current therapies shorten the duration of illness but do not improve survival (Coz Yataco and Simpson 2020). Therefore, naringenin could be employed as an immunomodulatory agent in SARS-CoV-2 infection, following further investigations.

An in vitro study on mouse adipocytes showed that hesperetin and naringenin downregulate the expression of TNF-α inflammatory mediator. This resulted in the inhibition of ERK and NF-κB pathways, leading to inhibition of IL-6 transcription (Yoshida et al. 2010). Further research study on rats suffering from acute lung injury indicated that hesperetin increases the expression of peroxisome proliferators activated receptor gamma. Subsequently, it inhibits the NF-κB pathway, results in a significant reduction in the production of inflammatory cytokines including IL-6, IL-1β, and TNF-α (Ma et al. 2015). Pre-treatment of acute lung injury (ALI) mice model by hesperetin caused a protective effect against pulmonary inflammation, meanwhile, hesperetin decreases the TNF-α and IL-6 expression (Ye et al. 2019).

Table 2 Immunomodulatory and anti-inflammatory effects of various flavonoid classes

Flavonoid	Immunomodulatory mechanism	References
Flavanones		
Naringenin	Inhibits ERK and NF-κB pathways, reduces COX-2, iNOS and TNF-α expression and reduces IL-6 and MPO activity	(Ali et al. 2017; Fouad et al. 2016; Yoshida et al. 2010)
Hesperetin	Inhibits ERK and NF-κB pathways, works as PPAR-γ agonist and reduces IL-6, IL-1β and TNF-α expression	(Ma et al. 2015; Ye et al. 2019; Yoshida et al. 2010)
Flavonoles		
Quercetin	Regulates Th1/Th2 balance, inhibits tyrosine phosphorylation of EGFR and NF-κB pathways and binds to aryl hydrocarbon receptor, and impairs T-cell activation	(Michalski et al. 2020; Park et al. 2009; Rogerio et al. 2010; Yang et al. 2012)
Fisetin	Inhibits NF-κB and phosphorylation of ERK1/2 pathways, inhibits PKC-δ activity, COX-2 and prostaglandin E2 production and decreases IL-6, IL-8, TNF-α, CCL5 and MPC1 levels	(Lee et al. 2018; Peng et al. 2018)
Flavones		
Chrysin	Inhibits NF-κB pathway, works as PPAR-γ agonist, inhibits COX-2 and MPO activity, inhibits TNF-α, IL-1β, IL-8 and iNOS levels, stimulates macrophage lysosomal activity, and inhibits the production of nitric oxide	(Sassi et al. 2017; Shen et al. 2015; Zeinali et al. 2017)
Apigenin	Inhibits IL-6, CCL5, ICAM1and VCAM1	(Zhang et al. 2014)
Luteolin	Increases the number of CD4$^+$CD25$^+$ regulatory T-cells, decreases the number of immune cells such as CD19$^+$B, CD4$^+$T, CD3$^-$CCR3$^+$ and CD11b$^+$Gr-1$^+$, inhibits MARK and NF-κB pathways, reduces TNF-α, IL-6, IL-1β levels and inhibits MPO activity	(Kim et al. 2018; Kuo et al. 2011; Liu et al. 2018)
Caflanone	Inhibits microsomal prostaglandin E synthase 1 and 5-lipoxyganse	(Erridge et al. 2020)

Flavonols: quercetin and fisetin

Quercetin caused inhibition of OVA-induced airway inflammation and leukocyte recruitment to the airways in murine mice asthma model (Park et al. 2009). Quercetin can regulate the Th1/ Th2 balance (Park et al. 2009). Oral administration of quercetin-loaded micro-emulsion in murine asthma model showed similar effects to dexamethasone, indicated by a significant reduction in mucus production in the lungs (Rogerio et al. 2010). Quercetin micro-emulsion also showed inhibition of NF-κB and selectively restrains Th2 cytokine (Rogerio et al. 2010). COVID-19 patients showed elevated MUC1 and MUC5AC mucin protein levels (Lu et al. 2020). Interestingly, quercetin inhibits tyrosine phosphorylation of EGFR and NF-κB pathways resulted in the suppression of mucin synthesis in rat lungs and reduction of MUC5AC in human airway epithelial NCI-H292 cells, and hence it reduces the mucus production and difficulty in breathing (Yang et al. 2012). Furthermore, quercetin exerts immunomodulatory effects on human dendritic cells (DCs) by direct the binding of aryl hydrocarbon receptor to CD83 promoter causing down expression of CD83 (Michalski et al. 2020). This impairs T-cell activation and migration of matured DCs (Michalski et al. 2020).

Fisetin showed significant anti-inflammatory and immunomodulatory effect. Pre-treatment of IL-1β-stimulated human lung epithelial cells with fisetin caused inhibition of COX-2 and reduction in IL-6, IL-8, TNF-α, CCL5, MCP1, and prostaglandin E2 (Peng et al. 2018). Fisetin also downregulates the NF-κB pathway and interferes with the phosphorylation of proteins in the ERK1/2 pathway, leading to a significant reduction in ICAM1 expression, which is involved in monocyte adhesion (Peng et al. 2018). Fisetin negatively modulates the PKC-δ activity in human airway epithelial cells, which is essential for the activation of the TNF-α/IKK/NF-κB signalling cascade (Lee et al. 2018). Inhibition of PKC-δ significantly reduces the TNF-α-induced IL-8 levels. Interestingly, fisetin has a similar effect to the broad protein kinase inhibitor, Staurosporine, hence it can be

employed as a potential immunomodulator in lung inflammation (Lee et al. 2018).

Flavones: Chrysin, apigenin, luteolin and caflanone

An extensive overview of immunomodulatory and anti-inflammatory effects of chrysin concluded that chrysin has multiple mechanisms. Chrysin can suppress NF-κB, which controls the expression of genes encoding the pro-inflammatory cytokines, COX-2 and iNOS (Zeinali et al. 2017). Besides, it is an agonist to PPAR-γ, which downregulates COX-2, MPO and iNOS (Zeinali et al. 2017). Pre-treatment of mice, exposed to cigarette smoking to induce inflammation of airway epithelial cells, with chrysin ameliorated the inflammation by suppressing the release of TNF-α, IL-1β, IL-8, and MPO expression in the lung tissue (Shen et al. 2015). Chrysin also inhibits ERK and p38 phosphorylation (Shen et al. 2015). In another study to analyse the immunomodulatory effect of chrysin on rat peritoneal macrophages, chrysin stimulates macrophage lysosomal activity, which involved in killing and digesting the microbial pathogens and inhibited the production of nitric oxide (Sassi et al. 2017). Docking study indicated that chrysin can bind weakly to COX-1, but strongly to COX-2 enzymes, indicating that it has relative selectivity to COX-2, and hence reduces the possibility of undesired GIT adverse effects (Rauf et al. 2015). Similarly, pre-treatment of pre-inflamed human macrophage with apigenin showed significant inhibition of IL-6 secretion and stability of IL-6 mRNA (Zhang et al. 2014). Apigenin did not inhibit only the pro-inflammatory cytokines, but also the inflammatory chemokines (CCL5) and adhesion molecules (ICAM1 and VCAM1) (Zhang et al. 2014).

Luteolin significantly increases the number of CD4 + CD25 + regulatory T-cells in murine splenic CD4 + -T cells that were stimulated by anti-CD3/anti-CD28 (Kim et al. 2018). Luteolin also presented immunomodulatory activity by decreasing the number of immune cells such as CD19 + B, CD4 + T, CD3-CCR3 + , and CD11b + Gr-1 + in the lung of inflamed airway mouse model (Kim et al. 2018). Luteolin also inhibits the NF-κB pathway, reduces TNF-α, IL-6, IL-1β levels and significantly inhibits MPO activity (Liu et al. 2018). Luteolin also showed a protective effect against lipopolysaccharides (LPS)-

induced ALI mice model by inhibition of MAPK pathways, leading to inhibition of the NF-κB pathway and IKB degradation (Kuo et al. 2011). Caflanone possesses anti-inflammatory activity by inhibition of microsomal prostaglandin E synthase 1 and 5-lipoxygenase (Erridge et al. 2020).

The data described here indicated the significant immunomodulatory activities of many flavonoids, while their antiviral activities still need to be validated to complement their potential inhibition activity against SARS-CoV-2.

Potential anti-SARS-CoV-2 activity of flavonoids in the case of complication by obesity

A case study of COVID-19 patients in Shenzhen, China concluded that obesity increases the risk of developing severe COVID-19 (Cai et al. 2020). Obesity may exacerbate infection by SARS-CoV-2 and can result in severe COVID-19 cases. An explanation for that can be attributed to the higher expression of ACE-2 in adipose tissues located in the lung (Jia et al. 2020). Furthermore, it has been shown that host lipids represent a critical factor in SARS-CoV-2 infection and completion of the life cycle (Alketbi et al., 2021).

Different studies indicated that flavonoids can be employed to reduce the body fat mass by generating a feeling of satiety by reducing the food intake (Panda and Shinde 2017). Flavonoid-rich foods can target the lipid-regulating enzymes and prevents lipid accumulation (Wu et al. 2010). Furthermore, flavonoids can reduce the weight of abdominal adipose tissue due to their effect on decreasing the hepatic and plasma triglyceride (TG) levels by regulating the rate-limiting enzymes involved in the fatty acid synthesis and oxidation in the liver (Kamisoyama et al. 2008). Interestingly, consuming tea catechin, a flavan-3-ol, is good for the suppression of high-fat diet-induced obesity via activation of lipid metabolism in the liver (Murase et al. 2002). Collectively, a diet rich in flavonoids can reduce the exacerbation of COVID-19 by reducing body fat mass, a factor that can increase SARS-CoV-2 load.

Table 3 Flavonoids LD_{50}

Flavonoids	LD_{50}	References
Naringenin	> 5000 mg/kg (Oral)	(Ortiz-Andrade et al. 2008)
Hesperidin	> 2000 mg/kg (Oral)	(Bigoniya and Singh 2014)
Quercetin	> 160 mg/kg (Oral)	(Sullivan et al. 1951)
Chrysin	= 4350 mg/kg (Oral)	(Yao et al. 2019)
Apigenin	> 5000 mg/kg (I.P.)	(Zarei et al. 2017)
Luteolin	> 5000 mg/kg (Oral)	(Liming 1985)

Safety and efficacy of flavonoids

Generally, flavonoids exhibit a high safety profile and LD_{50} as indicated in **Table 3**. It has been shown that oral administration of quercetin possesses no significant mutagenicity/ genotoxicity effects on mice and rats (Harwood et al. 2007). Quercetin is a well-tolerated compound and did not induce any adverse effects when administered orally and intravenously up to 1 g/day and at ∼ 10.8 mg/kg to human, respectively (Ferry et al. 1996; Shoskes et al. 1999). Similarly, oral administration of 450 mg citrus dry extract containing at least 90% of catechin of total polyphenols and at least 20% of naringenin of total flavanones to healthy overweight individuals did not induce any adverse effects (Dallas et al. 2014). No adverse effects have been observed in patients with muscular dystrophy when administered Flavomega, an oral dosage form that contains roots of *Scutellaria* and dry extract of green tea as a source of flavonoids (Sitzia et al. 2019). Intraperitoneal administration of apigenin, up to 100 mg/kg in mice does not induce any toxic effects (Viola et al. 1995).

The extent of absorption, distribution, metabolism and excretion of flavonoids are affecting its efficacy (Miranda et al. 2012). Different sources of flavonoids have different absorption and bioavailability (Ross and Kasum 2002). Sugar moiety attached to aglycone plays a major role in flavonoid absorption and bioavailability (Hollman 2009). Since most flavonoids found in diets are β-glycosides, they can be absorbed in two ways at the small intestine either by lactase phloridzin hydrolase (LPH) or intestinal Na^{+}- dependent glucose co-transporter (SGLT1) (Hollman 2009). Although flavonoids have poor oral absorption and bioavailability (Ross and Kasum 2002; Thilakarathna and Rupasinghe 2013) because of the hydrophilic nature of the flavonoid glycosides (Hollman 2009), the aglycones have a strong affinity to plasma; indicating

their activity at low concentration (Xiao and Kai 2012). Moreover, flavonoids undergo extensive metabolism in the intestine and liver leading to the formation of conjugated forms, which is increasing the ability of their elimination (Thilakarathna and Rupasinghe 2013). Therefore, the low bioavailability of flavonoids may hinder their oral administration (Thilakarathna and Rupasinghe 2013). On the other side, several approaches were employed to improve the bioavailability of the flavonoids including nano-formulations to improve the intestinal absorption, and microemulsions or complexing with β-cyclodextrin to improve the bioavailability (Thilakarathna and Rupasinghe 2013). Flavonoids encapsulated in smart nanoparticles with the ability to target ACE-2 receptors were administered by inhalation to mice to enhance their bioavailability and efficacy (Ngwa et al. 2020). Nano-emulsion and nano-liposomal formulations not only enhance the oral bioavailability of naringenin but also enhance the therapeutic efficacy and stability (Zobeiri et al. 2018). Fisetin encapsulation in nano-liposomal formulation enhanced the bioavailability by 47 folds when compared to free fisetin (Seguin et al. 2013).

Potential flavonoids with multi-targeting activity

According to the aforementioned data, one can conclude that flavonoids such as naringenin, apigenin, luteolin and quercetin can exert multiple activities as indicated in Table 4. Molecular docking studies of these flavonoids were further tested to validate the binding affinity to major targets including M^{pro}, ACE-2 and TMPRSS2 (Table 4 and Figs. 4, 5, 6). The 3D structures of flavonoids and 3D crystal structures of proteins were downloaded and saved in PDBQT format using Chimera software. The binding modes between the elected flavonoids and target proteins

Table 4 Potential flavonoids with dual activity against viral and human proteins

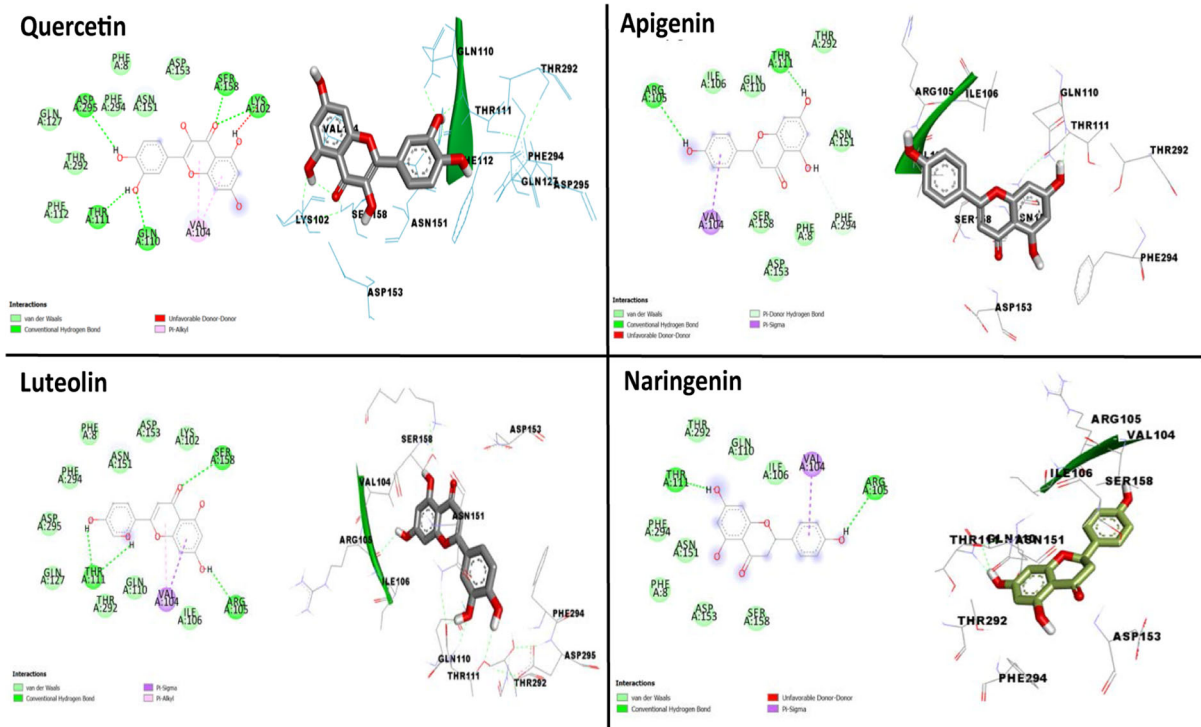| Flavonoid	Targets binding energy (Kcal/mol)				Immunomodulatory activity
	Host Target		Viral Target		
	ACE-2 receptor	TMPRSS2	M^{pro}	RdRp	
Quercetin	− 9.1	− 7.7	− 7.0	− 8.5	Anti-inflammatory
Luteolin	− 8.9	− 7.4	− 7.1	− 8.3	Reduces IL-6 expression
Apigenin	− 8.5	− 7.7	− 6.7	− 7.8	Inhibits IL-6
Naringenin	− 8.5	− 7.3	− 6.8	− 7.7	Reduces IL-6 expression
Enalaprilat	− 8.8				
Camostat		− 7.7			
GC376			− 6.0		
Remedisivir				− 8.9	

Fig. 4 Binding affinity of flavonoids to M^{pro}

were performed using PyRx Autodock binding engines. Flavonoids were screened against M^{pro} (PDB: 6LU7), TMPRSS2 (PDB: 2OQ5), ACE-2 (PDB: 1R4L),) and RdRp (PDB: 7BV2). The two-dimensional interaction with different amino acids was presented using Discovery Studio software.

The results indicated that quercetin and luteolin showed good binding energy with the binding pocket of M^{pro} (PDB: 6UL7) lower than that of GC376

inhibitor, indicating the formation of a stable complex. The superiority of quercetin and luteolin binding is due to the vicinal hydroxyl groups that act as metal chelators for the target enzyme (Fig. 4). Similarly, quercetin and luteolin showed good binding affinity to ACE-2 receptor with lower binding energy in comparison to enalaprilat (Fig. 5). Furthermore, quercetin and apigenin showed binding affinity to TMPRSS2 similar to Camostat (Fig. 6). The displayed binding
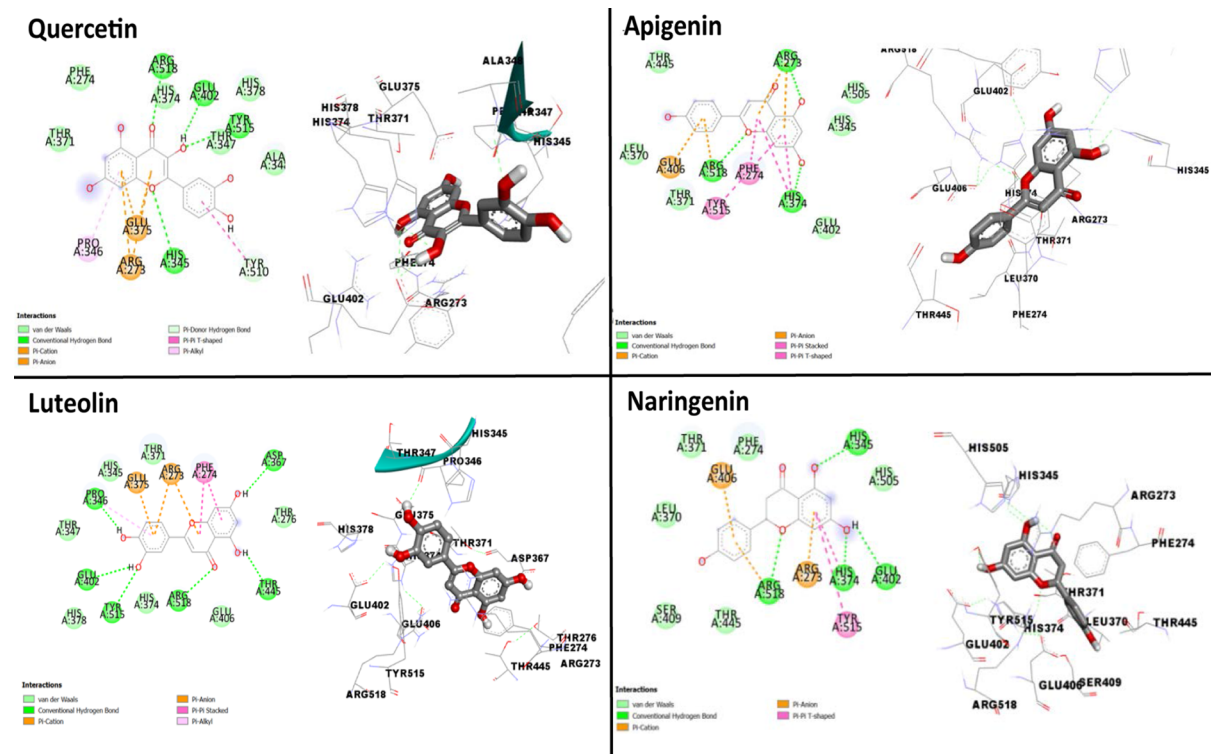
Fig. 5 Binding affinity of elected flavonoids to ACE-2 receptor

affinity of flavonoids is mainly owing to the hydrophobicity of the aromatic rings and the hydrophilic hydroxyl groups. However, they all showed lower binding affinity to RdRp when compared to remdesivir (Table 4).

The ADME properties were further screened using a Swiss-ADME server (Daina et al. 2017). The elected flavonoids comply with the Lipinski rule of 5 (HBD < 5, HBA < 10, Logp < 5, and Mwt < 500). The compounds showed good gastrointestinal adsorption, good solubility with log s < 4 and hence good bioavailability. Notably, they were safe and non-toxic (Fig. 7 and Table 5).

The results obtained highlight the importance of flavonoids as lead for the development of novel antiviral drugs. These flavonoids particularly quercetin and luteolin should be employed for further clinical investigations as a promising therapy against SARS-CoV-2.

Potential sources of flavonoids and environmental impact

Flavonoids are a large and diverse group of phenolic secondary metabolites widely distributed in plants. It has been reported that the richest sources of flavonols (Quercetin, kaempferol, and myricetin) are yellow onions (up to 1.2 g/kg fresh wt) and curly kale (up to 0.6 g/kg fresh wt) (Manach et al. 2004). Other sources with moderate levels of flavonols (0.1–0.225 g/kg fresh wt) are leeks, cherry tomato, broccoli, and blueberries (Manach et al. 2004). Furthermore, other sources with lower concentrations of flavonols were reported in black Curran, apricot, apple, red apple, beans, black grape, tomato, black and green tea (Manach et al. 2004). Flavones (apigenin and luteolin) present in parsley, celery, capsicum, and pepper. Flavanones such as hesperetin, naringenin, and eriodictyol are rich in tomatoes, orange, grapefruit, and lemon (Manach et al. 2004). Several other flavonoids have been identified in many wild plants such as *Atriplex hortensis, Betula alba, Brassica rapa, Ephedra alata, Hibiscus sabdariffa, Juniperus communis,*
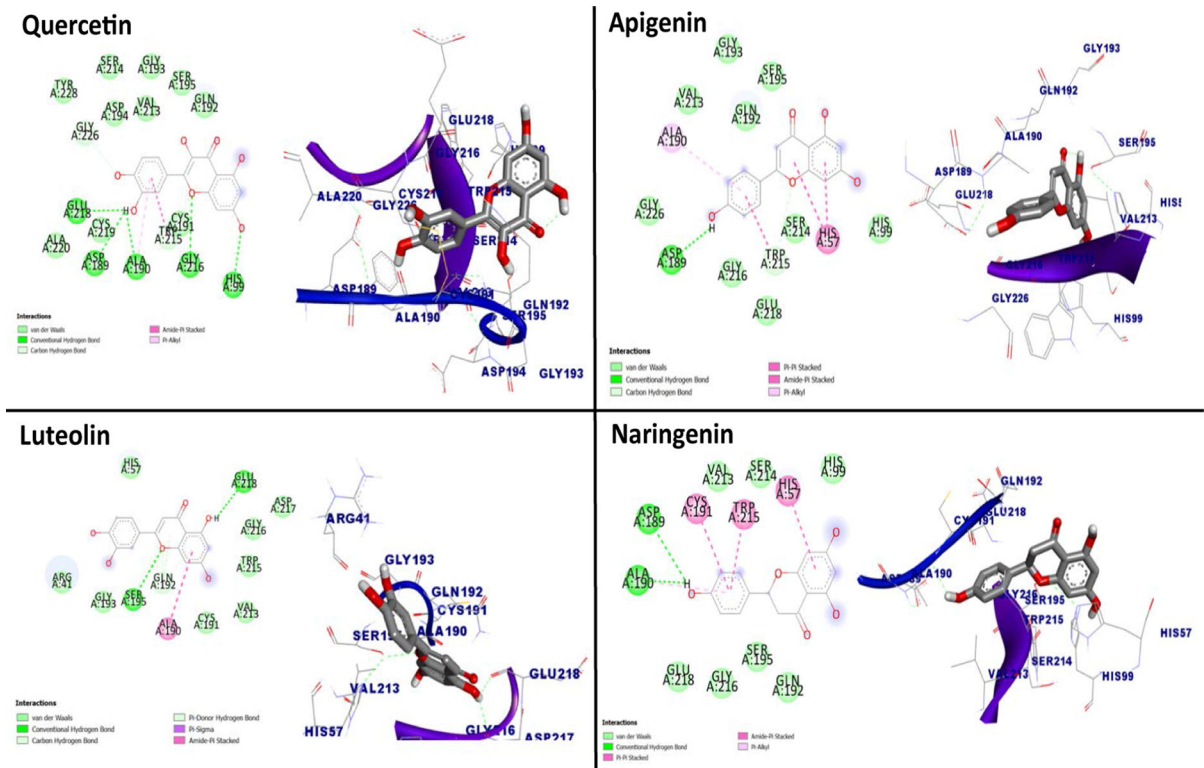
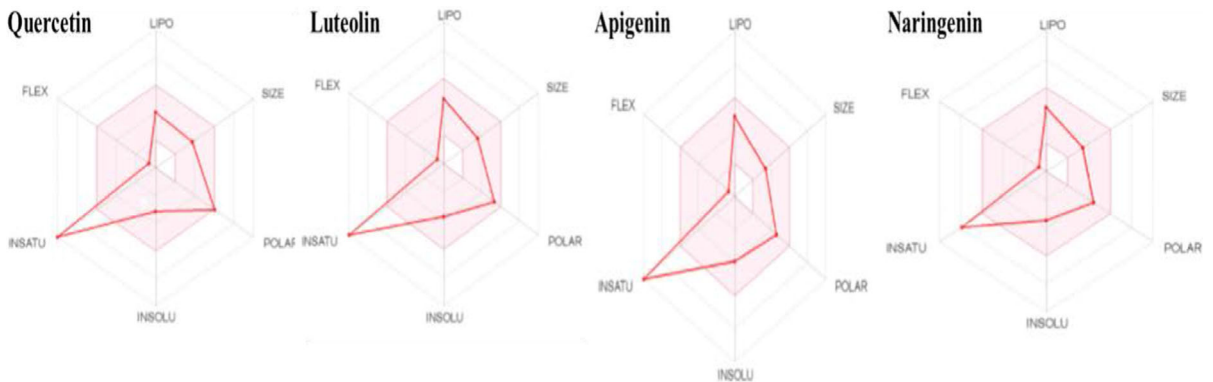**Fig. 6** Binding affinity of elected flavonoids to TMPRSS2

Fig. 7 Bioavailability radar of flavonoids. The figures indicated the acceptable pharmacokinetics and within conformity range. The pink area indicates preferred properties range

Antirrhinum majus, and *Artemisia campestris* (Al-Snafi 2020).

The types and concentration of flavonoids in plants are changed in response to the duration and frequency of environmental conditions associated with different geographic regions including the temperature, light duration, intensity and quality (Oh et al. 2009). Abouleish et al. 2020, showed that environmental factors can significantly affect the concentration and types of plant phytochemicals with potential activity against SARS-CoV-2 (Abouleish 2020). They have described the impact of the season, temperature, and drought on the yield and composition of plant phytochemicals including flavonoids. Besides, other environmental factors including the time of harvest, processing, and storage can affect the flavonoid

Table 5 Predication of ADME properties of elected flavonoids

Models	Quercetin	Luteolin	Apigenin	Naringenin
TPSA	131.6	111.13	90.9	90.9
Molecular formulae	$C_{15}H_{10}O_7$	$C_{15}H_{10}O_6$	$C_{15}H_{10}O_5$	$C_{15}H_{10}O_5$
Molecular weight	302.24	286.24	270.24	272.25
HBA	7	6	5	5
HBD	5	4	3	3
Log p	1.63	1.86	1.89	1.75
GI Absorption	High	High	High	High
Bioavailability score	0.55	0.55	0.55	0.55
P-glycoprotein Substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
BBB permeability	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes
Lead likeness violations	0	0	0	0
Synthetic accessibility	3.23	3.02	2.96	3.01
No of rotatable H bond	1	1	1	1
ESOL solubility	Soluble	Soluble	Soluble	Soluble
Solubility (mg/mL)	0.211	0.0563	0.0307	0.0874
Log s	− 3.16	− 3.71	− 3.94	− 3.49

contents in medicinal plants (El-Keblawy et al. 2017; Manach et al. 2004). Therefore, assessing the impact of environmental conditions on plant flavonoids can help in the selection of the most suitable flavonoid-rich plants per geographical area (Sehlakgwe et al. 2020).

The most common and richest sources with several types of flavonoids for human intake are citrus and black and green teas (Manach et al. 2004). The intake of these plants was recommended as a therapy for COVID-19. Several investigators have indicated that environmental factors prevailing during the growth and development of citrus (Zandalinas et al. 2017) and

tea (Table 6) can affect the types and accumulation of different flavonoids.

Global intake of flavonoids

The intake of flavonoids differs from a country to another. This is mainly due to the difference in the type and amount of food rich in flavonoids taken in each country (Table 7 and Fig. 8). The worldwide consumption of flavonoids ranges between 150–600 mg/day expressed as aglycones present in

Table 6 Effect of environmental factors on the flavonoid contents in tea leaves (*Camellia sinensis*)

Region/country	Environmental condition	Flavonoid content	References
Jeju Island, South Korea	High temperature	Low	(Lee et al. 2010)
Malawi	High temperature	Low	(Owuor et al. 2008)
Phoenix Mountain, China	High altitude	High	(Chen et al. 2010)
Phoenix Mountain, China	Autumn growing season	High	(Chen et al. 2010)
Australia	Warm growing season	High	(Yao et al. 2005)
Seogwipo Si, Republic of Korea	High light intensity	High	(Ku et al. 2010)
Barcelona, Spain	Drought	High	(Hernández et al. 2006)
Anhui, China	High temperature	High	(Wang et al. 2012)
Anhui, China	Drought	High	(Wang et al. 2012)

Table 7 Intake of total flavonoids in representative countries

Country	Intake (mg/day)	Main source	Major class	Reference
Australia	225	Black tea	Flavanols	(Johannot and Somerset 2006)
Spain	443	Fruits	PA	(Tresserra-Rimbau et al. 2013)
Italy	364	Fruits	PA	(Vitale et al. 2018)
France	436	Fruits, tea, red wine	PA	(Perez-Jimenez et al. 2011)
Finland	209	Berries, fruit	PA	(Ovaskainen et al. 2008a, b)
Poland	898	Tea, cocoa, apples	Flavanols	(Grosso et al. 2014)
United Kingdom	1000	Tea	Flavanols, PA	(Tresserra-Rimbau et al. 2013)
US	203	Tea	Flavanols, PA	(Xiao et al. 2014)
Mexico	235	Fruits and orange	PA	(Zamora-Ros et al. 2018)
Brazil	54.6	Citrus fruits and beans	Flavanones	(Miranda et al. 2016)
China	225	Soy, pome fruit	Flavanols	(Zhang et al. 2014)
Korea	318	Fruit, tofu, onions	PA	(Jun et al. 2016)
Iran	1652	Vegetables, fruits	Flavanols	(Sohrab et al. 2013)
MED	449	Fruits	PA	(Zamora-Ros et al. 2016)
Non-MED	522	Fruits-black tea	PA	(Zamora-Ros et al. 2016)

MED = Mediterranean countries; Non-MED = Non-Mediterranean countries; PA = Proanthocyanidins
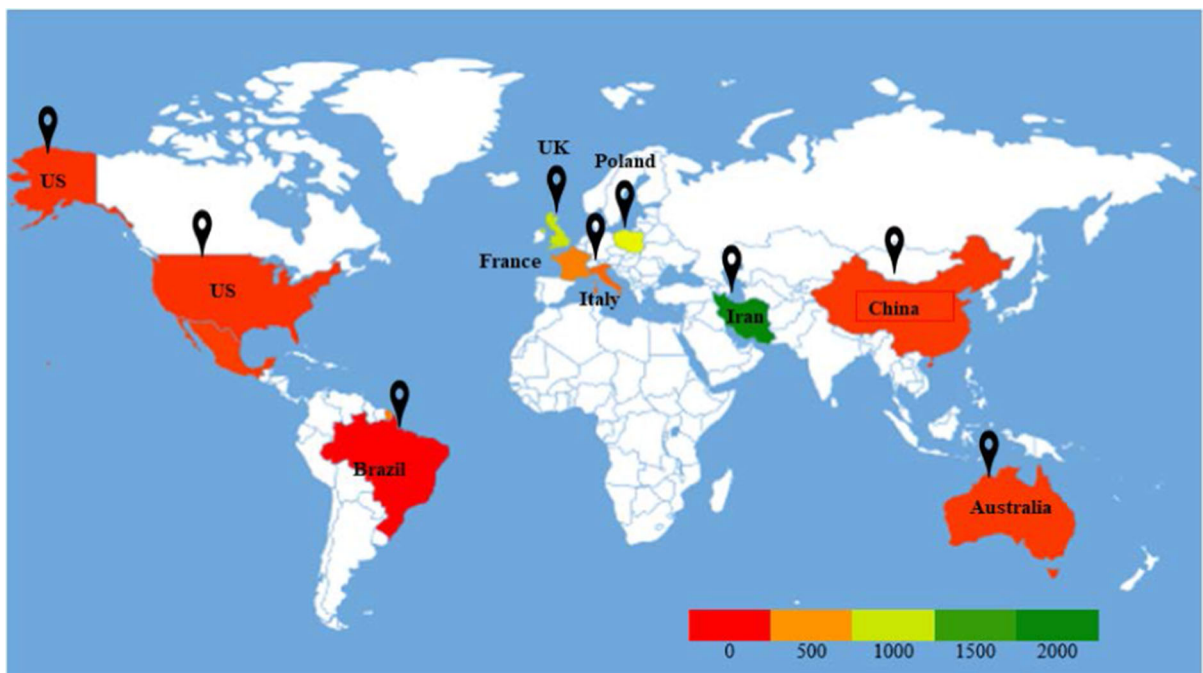

Fig. 8 Global heat map indicated the consumption of flavonoid-rich foods in representative countries. The heat map was generated by reporting the consumption of flavonoids per country (ElDohaji et al. 2020)

black tea(Zamora-Ros et al. 2016). This is varied between populations according to the black tea consumption levels and various dietary patterns. The intake of flavonoids varies greatly by geographical region (Tresserra-Rimbau et al. 2013). The intake of total flavonoids in European countries ranges between

250–400 mg/day, which is lower than in non-Mediterranean (MED, northern European) countries (350–600 mg/day). This can be attributed to the higher intake of tea in non-MED countries relative to MED countries (Tresserra-Rimbau et al. 2013). In Mediterranean countries, like Spain, the major polyphenols source in the diet is the fruits and coffee, but the factor that mainly differentiates them from other countries is the consumption of polyphenolics from olive oil and olives(Tresserra-Rimbau et al. 2013). Because of the conventional tea community, the highest overall flavonoids consumption in Europe is in the UK (~ 500 to > 1000 mg/day) (Zamora-Ros et al. 2016). On the other hand, Eastern European countries such as Poland showed a high intake of total flavonoids (600 mg/day) due to the high consumption of tea (Zamora-Ros et al. 2013), while the southern regions such as France has an intermediate intake of total flavonoids (Witkowska et al. 2015). The intake of total flavonoids in Scandinavian countries, such as Finland, is 200–250 mg/day, which is lower than in MED countries, because of lower tea and fruit consumption (Ovaskainen et al. 2008a, b).

Australia has a high intake of total flavonoids (650–700 mg/day), because of high tea consumption. Black tea consumption contributes to at least 75% of total polyphenols (Kent et al. 2015). The mean intake of total flavonoids in the US ranges from 250 to 400 mg/day (Kim et al. 2016). Although tea consumption is not very high, tea is still the primary source of total flavonoids in the US, possibly due to the low fruit and vegetable consumption. In Mexico and Brazil, the consumption of total flavonoids is about 150 and 50 mg/day, respectively. These countries are known globally as the lowest consumers of total flavonoids. Citrus in Mexico and beans in Brazil are the primary source of total flavonoids (Miranda et al. 2016).

In the Eastern Asian countries, such as China(Zhang et al. 2014), total flavonoids intake ranges between 65–225 mg/day (Zhang et al. 2014), since Chinese people drink green tea, but not black tea. The consumption of total flavonoids is significantly higher in South Korea (320 mg/day) (Chun et al. 2007). Soy and its derived products (the major food sources of isoflavones) are one of the most significant contributors to total flavonoids in East Asian countries, while proanthocyanidins and flavan-3-ol in South Korea and China are the most abundant flavonoids. Japan, China

and South Korea depend on isoflavones as a source of flavonoids, because of their phytoestrogenic effects (Barnes 2004). On the other hand, the mean intake of total flavonoids in the Middle East was estimated at 1650 mg/day (Sohrab et al. 2013). This is the world's highest cumulative consumption of flavonoids, which is attributed to the high consumption of black tea.

In summary, there is high variability in the total flavonoids intake between different countries. Those with high consumption of tea, especially black tea, are the populations with a higher intake of total flavonoids. Fruits are the primary food sources, and proanthocyanidins are the main contributors to total flavonoids. There is a need for more studies on the content of flavonoids in foods to enhance the existing data regarding the food composition and their role/relation in fighting against pathogens including SARS-CoV-2.

Suggested regimen of globally existed flavonoid-rich plants

Based on the aforementioned data described here for the possible use of flavonoids as a treatment and protection against SARS-CoV-2, we are suggesting a protective and treatment regimen made of easily accessible plants and globally distributed. For example, fresh parsley (*Petroselinum crispum*), raw wild rocket (*Diplotaxis tenuifolia*) and raw oranges are globally accessible vegetables and fruits. Interestingly, they contain significant amounts of flavonoids. Fresh parsley contains 215.45 mg/100 g apigenin and 1.09 mg/100 g luteolin, raw wild rocket contains 66.19 mg/100 g quercetin and raw orange contains 27.25 mg/100 g hesperetin and 15.32 mg/100 g naringenin (Haytowitz 2018). Therefore, a regimen made of oranges with 420 g total weight, 300 g fresh parsley and 300 g raw rocket per day would supplement a total of ~ 1 g flavonoids sufficient for the protection and treatment of SARS-CoV-2 infection (Di Matteo et al. 2020). This suggested regimen is still under investigation and needs further confirmation by clinical trials on COVID-19 patients. Current clinical trials employing 1000 mg/day of quercetin as a treatment and 500 mg/day as prophylaxis against SARS-CoV-2 infection are in the investigation process (Di Matteo et al. 2020).

Conclusion

Consumption of flavonoids and flavonoids-rich plants can be of significant importance for the prevention and treatment of SARS-CoV-2, while providing enough safety on the human body. In fact, flavonoids have been shown to exhibit potential inhibitory activity against critical viral targets, required to facilitate their entry and replication, including M^{pro}, RBD of the S protein, RdRp, in addition to the human ACE-2 receptor and TMPRSS2. Further, the immunomodulatory activity of flavonoids has been proven via the inhibition of various pro-inflammatory cytokines and pathways involved in inflammatory reactions. Furthermore, flavonoids can reduce the COVID-19 exacerbation via their significant effect on the body fat mass. Flavonoids promote the satiety effect and lipids metabolism. Based on the global existence of flavonoid-rich plants, a preventive safe regimen can be recommended against SARS-CoV-2 following further clinical investigations.

Declarations

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