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Flavonols as potential antiviral drugs targeting SARS-CoV-2 proteases (3CL^{pro} and PL^{pro}), spike protein, RNA-dependent RNA polymerase (RdRp) and angiotensin-converting enzyme II receptor (ACE2)

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ABSTRACT

The novel coronavirus outbreak (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the actual greatest global public health crisis. The lack of efficacious drugs and vaccines against this viral infection created a challenge for scientific researchers in order to find effective solutions. One of the promising therapeutic approaches is the search for bioactive molecules with few side effects that display antiviral properties in natural sources like medicinal plants and vegetables. Several computational and experimental studies indicated that flavonoids especially flavonols and their derivatives constitute effective viral enzyme inhibitors and possess interesting antiviral activities. In this context, the present study reviews the efficacy of many dietary flavonols as potential antiviral drugs targeting the SARS-CoV-2 enzymes and proteins including Chymotrypsin-Like Protease (3CL^{pro}), Papain Like protease (PL^{pro}), Spike protein (S protein) and RNA-dependent RNA polymerase (RdRp), and also their ability to interact with the angiotensin-converting enzyme II (ACE2) receptor. The relationship between flavonol structures and their SARS-CoV-2 antiviral effects were discussed. On the other hand, the immunomodulatory, the anti-inflammatory and the antiviral effects of secondary metabolites from this class of flavonoids were reported. Also, their bioavailability limitations and toxicity were predicted.

1. SARS-CoV-2 infection

The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China in December 2019, and spread around the world. This viral infection declared as a pandemic by the World Health Organization in March of 2020 constitutes the actual greatest global public health crisis and presents a challenge for the scientific society in order to find effective drugs for its prevention and treatment.

The SARS-CoV-2 has been identified as β-coronavirus, a non-segmented enveloped positive-sense RNA virus with a crown-like appearance and a symmetric helical nucleocapsid (Astuti, 2020). This virus is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses (Shang et al., 2020). Therefore, bats could constitute its primary zoonotic reservoir, the intermediate source of transfer to humans is not well-known but probable pangolin origin was reported (Zhang et al., 2020a; Lam et al., 2020). However, the rapid human to human transfer is well documented. Indeed, this disease is transmitted by inhalation of infected droplets or by contact with contaminated surfaces or patients (Van Doremalen et al., 2020). The virus genome encodes twenty different proteins including four main structural proteins (S: spike; E: envelope; M: membrane; N: nucleocapsid), and many nonstructural proteins including coronavirus main protease (3CL^{pro} or M^{pro}), RdRp and PL^{pro} (Mousavizadeh and Ghasemi, 2020).

Cellular infection and replication cycles start after the penetration of the virus in the host cells. The ACE2 is a type 1 transmembrane metallocarboxypeptidase that modulates the renin-angiotensin system (RAS) frequently expressed in the alveolar epithelial cells and many other tissues (Turner et al., 2002). This enzyme constitutes the key functional receptor for the SARS-CoV-2 that allows the attachment to human and

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bat cells (Walls et al., 2020; Sigrist et al., 2020). Indeed, this receptor combines with spike protein-receptor binding domain (RBD) (S1 subunit), and the interaction trigger conformational changes of the C-terminal of the S protein inducing the exposition of S2 subunit responsible for virus-cell membrane fusion. The fusion process requires activation by proteolysis in S1/S2 junction processed by host cell-type-II transmembrane serine protease (TMPRSS2) leading to the ACE2 cleavage and therefore to viral endocytosis (Lan et al., 2020; Rabby, 2020). The binding affinity between ACE2 and the ectodomain structure of the S protein determines the human transmission capability and inflammatory response. It is supposed that the decrease of ACE2 activity and expression in host-cell membranes reduce the entrance ability and the inflammatory activity (Letko et al., 2020). After the endocytosis and uncoating process, the genomic RNA released in the cytoplasm is translated into two polyproteins (pp1a and pp1ab) by host ribosomes. These polyproteins undergo a proteolytic cleavage generating 15–16 nonstructural proteins including two cysteine proteases PL^{pro} and $3CL^{pro}$. These proteases are key tools for the auto cleavage process which is essential for viral propagation and infection cycle (Hamid et al., 2020). The set of non-structural proteins (nsp) produced assemble to facilitate viral replication and transcription and constitute a multi-subunit replication/transcription machinery. The nsp12 also known as RdRp is a crucial replicate that catalyzes the synthesis of a complementary RNA strand using the virus RNA template with the assistance of nsp7 and nsp8 as co-factors (Huang et al., 2020). The genomic RNA is also transcribed into subgenomic RNA which in turn leads to the synthesis of structural (S, E, M and N) and accessory proteins. That subsequently insulated in the endoplasmic reticulum and then moved to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Finally, the assembled virions are released via the secretory pathway (Astuti, 2020).

2. Infection symptoms

SARS-CoV-2 viral infection can be divided into three stages: asymptomatic period, non-severe symptomatic period, and the severe infection stage. The infection symptoms appear after an incubation period of 5–6 days and the rapidity of symptoms appearence depends on patient's immune system and age (Skariyachan et al., 2019; Hamid et al., 2020). The infected patients suffer usually from fever, dry cough, sore throat, myalgia, dyspnoea, tiredness, malaise among other less common symptoms including headache, abdominal pain, diarrhea, nausea, and vomiting (Song et al., 2020). This disease is mild in most young and healthy people. However, in cases of the elderly and those with comorbidities, and chronic diseases (hypertension, diabetes, respiratory system and cardiovascular diseases), it may progress to acute respiratory distress syndrome (ARDS), pneumonia, acute renal and cardiac injuries and septic shock. Many people are asymptomatic and maybe just silent carriers of the virus (Liu et al., 2020; Morley and Vellas, 2020; Li and Xu, 2020).

3. Diagnosis

Diagnosis is performed by the combination of many tests starting with common laboratory analysis of white cell counts and C-reactive protein (CRP) level (Lagunas-Rangel, 2020; Ling, 2020). Virus demonstration in respiratory or blood specimens by special molecular and serological assays including the reverse-transcription polymerase chain reaction tests (RT-PCR), gene sequencing and the enzyme-linked immunoassay (ELISA) for specific IgM and IgG antibodies (Zhong et al., 2020). The high cost of ELISA test and the low sensitivity of RT-PCR due to problems with sample collection and transportation, RNA extraction, implies that many COVID-19 patients are not identified (false-negative cases) and do not receive the appropriate treatment in time and constitute a high risk of contagiously to the population. For this, as an important complement to RT-PCR, Chest CT scan is used. This routine imaging tool for pneumonia diagnosis is a performing manner to produce a fast diagnosis for COVID-19 (Ai et al., 2020; Fang et al., 2020).

3.1. Current treatments and prevention approches

No special available antiviral drugs or vaccines against coronavirus disease were clinically approved. Actually, The treatment is symptomatic and based on the use of broad-spectrum antiviral drugs and immunomodulating therapies (Remdesivir, Favipiravir, Lopinavir-Ritonavir, Hydroxychloroquine and Chloroquine, etc., …) (Rabby, 2020). The supplementation with micronutrients and vitamins improves clinical recovery. Vitamins D and C play a crucial role in the reduction of respiratory tract infections risks by minimizing viral replication rates and the concentrations of pro-inflammatory cytokines. These vitamins enhance the antioxidant response by the neutralization of reactive oxygen species (ROS), activate the innate immune response and assist immunoregulation (Grant et al., 2020; Zhang et al., 2020b). Many other approaches for the treatment were applied including the serum therapy and antibody medicine (Law, 2020). The injection of blood plasma from clinically recovered patients of COVID-19 to infected patients significantly reduced the period of recovery. Monoclonal antibodies able to bind with the S proteins of SARS-CoV-2 constitute a potential therapeutic candidate for the prevention and treatment of COVID-19 infection (Wang et al., 2020a). Coagulopathy in cases of ARDS associated to the increase in D-dimers and fibrinogen is managed with anticoagulant and antithrombotic therapy (Mezalek et al., 2020). Oxygen therapy is the major treatment intervention for patients with severe infection. While the mechanical ventilation is necessary in cases of respiratory failure refractory to oxygen therapy (Wilcox, 2020). However, preventive care could curb the spreadability of infection. According to the World Health Organization (2014), the improvement of hand hygiene practices, the use of personal protective equipments (face masks/respirators, gloves, goggles/face shields, and gowns) and surfaces disinfection reduce the human to human transmission risks (Pradhan et al., 2020).

4. Flavonols and Covid-19

One of the promising therapeutic strategies against Covid-19 virus infection is the search for enzyme inhibitors in natural compounds using molecular docking in order to obtain products with minimal side effects. 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) (Karak, 2019; Rengasamy et al., 2019; Lalani and Poh, 2020). 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 (Boukhatem and Setzer, 2020; Panche et al., 2016). Flavonol is one of the most important classes of flavonoids characterized by a hydroxyl group in C-3 position of the C ring. According to data analysis, flavonols constitute the most studied compounds against coronavirus (Russo et al., 2020; Muchtaridi et al., 2020; Jo et al., 2020; Gorla et al., 2020). Indeed, kaempferol, quercetin, myricetin, fisetin and their derivatives were the most documented molecules with antiviral activities against SARS-CoV-2 (Fig. 1.). Also, these molecules had a broad spectrum of biological activities (anti-HIV, antioxidant, anti-inflammatory and cardiovascular protective effects), that could reduce the severity of infection symptoms and enhance the immune response of the patient (Sharma et al., 2018; Zaragozá et al., 2020; Nakanishi et al., 2020).

The present study reviews the efficacy of many dietary flavonols as potential antiviral drugs targeting the SARS-CoV-2 enzymes. Papers recently published (from January to August 2020) in PubMed, Google Scholar, and Science Direct databases were selected for data extraction. Firstly, All articles evaluating the effects of flavonoids on COVID-19 infection, written in English language and containing the following

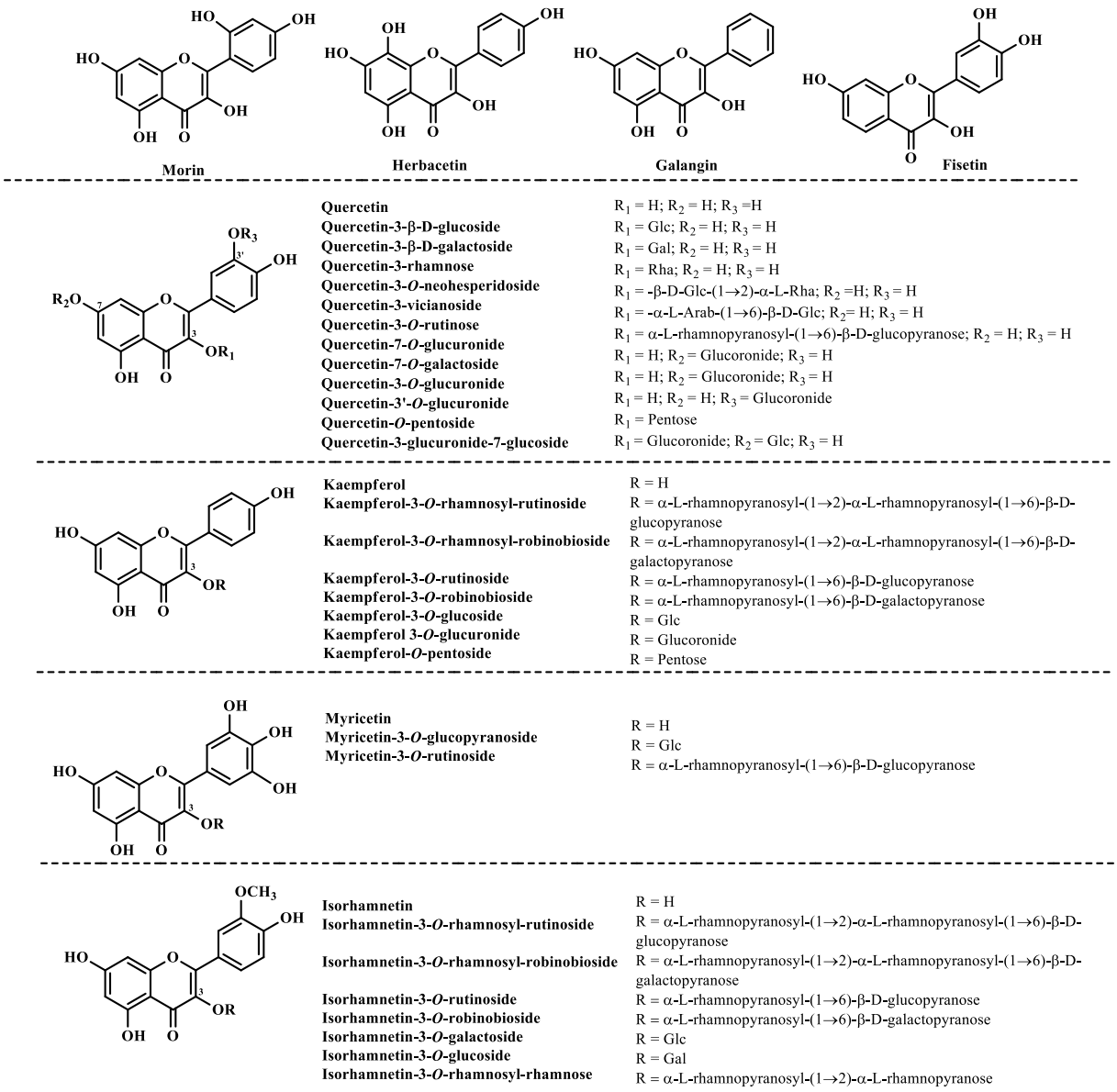

Fig. 1. Structures of flavonols possessing COVID-19 antiviral effects.

keywords: COVID-19, viral infection, flavonoids, flavonols, docking, *in silico*, M^{pro}, $3CL^{pro}$, PL^{pro}, RdRp, S protein, and ACE2 receptor were researched and selected regardless of publication types. Then, the results of the initial search were filtered by the lecture of their title and abstract. Studies with insufficient or duplicated information were excluded from the review. After the first selection, the full texts of the selected papers were read and only eligible and pertinent articles containing information about flavonols were included and chosen for data extraction. All the selected flavonols in the chosen data were cited in the library of natural products based on adherence to Lipinski's rule of five and Veber's Rule, and also for their antiviral, anti-inflammatory, immunomodulatory, and protective effects.

4.1. Antiviral, anti-inflammatory and immunomodulatory effects of flavonols

Many studies demonstrated the important antiviral activity of flavonols as secondary metabolites. Indeed, these molecules can interfere the pathology process at multiple levels and disturb the virus's entry and the replication cycle. Many aglycone and mono-glycoside flavonols have strong antiviral activities against influenza A and B viruses including fisetin, quercetin, rutin and isoquercetin (Enkhtaivan et al., 2017; Kim et al., 2010). Morin, galangin, quercetin, kaempferol, and myricetin had a board antiviral effects against a variety of viruses including poliovirus type 1, HSV-1 and 2, respiratory syncytial virus (RSV), Coxsackie B virus type 1, HCV, Canine distemper virus, SARS-CoV, and HIV-1 viruses (Zakaryan et al., 2017), human rhinovirus (HRV) (Kwon et al., 2020), Enterovirus A71 (EV-A71) (Lalani and Poh, 2020) and severe fever with thrombocytopenia syndrome virus (SFTS) (Ogawa et al., 2020).

Quercetin and its glycosylated analogs, especially those substituted at C-3 and C-7 positions and those with an additional hydroxyl group in A ring, are considered as potent antiretroviral agents. Indeed, herbacitrin and quercetin had strong antiviral activities against human immunodeficiency virus type 1 (HIV-1) (Áy et al., 2019). Quercetin had potent antiviral activities towards a wide range of viruses such as Human Herpesviruses (Kim et al., 2020), the dengue virus type-2 and hepatitis C virus (Batiha et al., 2020). Isoquercitrin (quercetin-3-*O*-glucoside) displayed a potent antiviral activity against varicella-zoster virus (VZV), human cytomegalovirus (HCMV) (Kim et al., 2020), ebola (Qiu et al., 2016) and influenza viruses (Kim et al., 2010). According to the study of

Dayem et al. (2015) isorhamnetin had stronger antiviral effect compared to quercetin and kaempferol due to the presence of a supplementary methyl group on C-3′ position in B ring.

The intense and the rapid stimulation of the innate immune response after the infection with SARS-CoV-2 virus triggers the activation of the Nod-like receptor family and pyrin domain-containing 3 (NLRP3) inflammasome pathway inducing the release of many proinflammatory cytokines mainly IL-6 and IL-1β. This dysregulated hyper-inflammation is responsible of the complications associated to this infection including the severe lungs tissues injury (Freeman and Swartz, 2020; Van Den Berg and Te Velde, 2020). For this, molecules able to modulate this dysregulated response could constitute effective drugs beneficial for the treatment of the cytokine storm syndrome associated to the Covid-19 infection (Mehta et al., 2020). Several flavonols including fisetin, kaempferol, myricetin, astragalin, and rutin could induce the inhibition of cytokines expression and synthesis (Higa et al., 2003). Quercetin had an immunosuppressor effect, this molecule inhibits IL-1β, TNF-α, IL-6, and IL-8 in LPS-stimulated whole blood production (Zaragozá et al., 2020), and induces the suppression of NLRP3 inflammasome activation (Owona et al., 2020). Also, the coadministration of vitamin C and quercetin enhances the antiviral response and induces an immunomodulatory regulation that is beneficial for the treatment of respiratory tract infections (Colunga Biancatelli et al., 2020). Morin was reported for its useful effects on acute lung injury by the inhibition of NLRP3 inflammasome (Tianzhu et al., 2014; Dhanasekar and Rasool, 2016).

Quercetin decreases the clinical signs of chronic arthritis induced by adjuvant in rats (Mamani-Matsuda et al., 2006) and improves the inflammatory response (Morikawa et al., 2003). According to Makino et al. (2013), glycosyl conjugation with specific sugar units enhances *in vivo* biological activities of quercetin. Indeed, quercetin-3-*O*-glucuronide had potent immunomodulatory and anti-atherogenic activities (Derlindati et al., 2012) and exerted an interesting anti-inflammatory effect by the suppression of JNK and ERK signaling pathways (Park et al., 2016). Isorhamnetin contributes to the inhibition of acute inflammatory response by the inhibition of JNK and AKT/IKKα/β pathways activation which leads to NF-κB inactivation (Yang et al., 2013). This metabolite inhibits the reactive oxygen species production induced by LPS and acts as a natural COX-2 inhibitor (Seo et al., 2014). Isorhamnetin and its sulfate derivative persicarin possess antithrombotic and anticoagulant activities (Ku et al., 2013). Isorhamnetin-3-*O*-glucosyl-rhamnosyl-rhamnoside and isorhamnetin-3-*O*-glucosyl-rhamnoside exhibit significant anti-inflammatory effects by several mechanisms of action including the regulation of cytokines secretion, the suppression of cellular infiltration, and the inhibition of nitric oxide production and COX-2 activity. However, isorhamnetin-3-*O*-glucosyl-rhamnosyl-rhamnoside is less active than isorhamnetin-3-*O*-glucosyl-rhamnoside, suggesting that the glycosylation profile affects the bioactivity (Antunes-Ricardo et al., 2015). Kaempferol-3-*O*-glucorhamnoside has a potent anti-inflammatory effect *in vitro* and *in vivo* (Sun et al., 2019a). The anti-inflammatory activity of myricetin was reported in several studies on animal models *in vitro* and *in vivo* (Semwal et al., 2016; Wang et al., 2010). In fact, this molecule showed a high anti-inflammatory activity against the *Porphyromonas gingivalis*-induced inflammatory response in host cells and prevented NF-κB activation in a monocyte model. In addition, this molecule inhibited the secretion of many cytokines including IL-6 and IL-8 (Grenier et al., 2015).

4.2. Flavonols targeting $3CL^{pro}$ and PL^{pro}

$3CL^{pro}$, also known as the main protease (M^{pro}) is a non-structural protein encoded by the SARS-CoV-2 genome. This enzyme is required for proteolytic maturation of the viral polyproteins (pp1a and pp1ab) in order to form the RNA replicase-transcriptase complex, which is essential for both viral transcription and replication processes (Elmezayen et al., 2020). This protease has a highly conserved three-dimensional structure among various CoVs and active only in a dimeric form (the individual monomers of SARS-CoV M^{pro} are enzymatically inactive). Structural and catalytic characteristics of the $3CL^{pro}$ make it a selective target for drug development. Indeed, many strategies could be employed in order to develop inhibitors against this enzyme. Firstly, since M^{pro} is highly conserved, a mutation in M^{pro} genome is often lethal to the virus, the catalytic activity of this enzyme could be altered by the fixation of a molecule in the substrate-binding pocket or by the use of dimerization inhibitors (Gyebi et al., 2020; Goyal and Goyal, 2020; Khaerunnisa et al., 2020). Thus, molecules targeting the M^{pro} enzyme may constitute promising drugs with a broad-spectrum of antiviral activities able to stop the post-translational processing of SARS-CoV-2 polypeptides and to reduce the risk of mutation-mediated drug resistance.

PL^{pro} is another important druggable target due to its important functions in the viral replication cycle. This enzyme is involved in N-terminal viral polyproteins cleavage in order to generate many Nsps (Nsp1, Nsp2, and Nsp3) (Mhatre et al., 2020). It is also crucial in alienating the innate immunity of the host cells. Indeed, SARS-CoV viruses use PL^{pro} as an antagonist to inhibit the activation of the interferon regulatory factor-3 pathway (IRF3-pathway) in order to reduce the production of interferon widely known for its antiviral activities (Chen et al., 2014; Yuan et al., 2015). For this, the inhibition of PL^{pro} enzyme would normally elicit a robust interferon-mediated response, activate the immune system and the antiviral response of the host cells, and also disturb the replication cycle.

Flavonols could be considered as promoter compounds able to induce the inhibition of many enzymes involved in the infection with coronavirus and constitute a source of possible drugs and vaccines candidate against this pandemic. According to the study of Nguyen et al. (2012), the lack of 2,3-double bond and carbonyl group at the C-4 position in the C ring, and galloyl moiety and the presence of hydroxyl group in C-5′ position of B ring in flavonoid skeletons reduce the chemical interactions, the formation of hydrogen bonds and the electrostatic interactions with the active site of $3CL^{pro}$. These data support the bioactivity of flavanols which contain a carbonyl function (C-4) and a double bond in position C_2–C_3 compared to other classes of flavonoids. Owis et al. (2020) reported the molecular docking and the different interactions between the N3 binding site in the main protease and eleven flavonol glycosides namely kaempferol-3-*O*-rhamnosyl-rutinoside, kaempferol-3-*O*-rhamnosyl-robinobioside (mauritianin), isorhamnetin-3-*O*-rhamnosylrutinoside, isorhamnetin-3-*O*-rhamnosyl-robinobioside, isorhamnetin-3-*O*-rutinoside (narcissin), isorhamnetin-3-*O*-robinobioside, kaempferol-3-*O*-rutinoside, kaempferol-3-*O*-robinobioside, isorhamnetin-3-*O*-glucoside, isorhamnetin-3-*O*-galactoside and kaempferol-3-*O*-glucoside (astragalin) obtained from the aqueous fraction of *Salvadora persica* L. aerial parts. The data showed that all the tested flavonols had significant binding stability compared to the darunavir as standard drug, which confirms that the basic flavonol skeleton itself possesses an activity. The comparison between these results revealed that the presence of rutinose moiety (α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose) at the C-3 position of C ring and the absence of an additional methoxyl group at C-3′ position of B ring in flavonol structure could increase the binding stability. Furthermore, the addition of a rhamnose unit to the rutinoside group decreases the binding stability of the tested molecules (Owis et al., 2020). This could be explained by the covering of specific hydroxyl groups in the tested molecule with adjacent groups, preventing the ability of hydrogen bond formation and electrostatic interactions by steric blocking. Also, from the study of Cherrak et al. (2020), seventeen flavonol glycosides were modeling for their ability to interact with the active site of the M^{pro}. Among these compounds, five molecules namely quercetin-3-*O*-rhamnose, myricetin-3-*O*-rutinoside, rutin, myricitrin and quercetin-3-*O*-neohesperidoside had strong docking scores. Glycoside flavonols had a high binding affinity than aglycone flavonols. In fact, for aglycone skeletons, the C-3 substituted

flavonols were more active than those substituted in C-7 position. In the case of glycosylated flavonols, the nature of the linked sugar with the skeletons and its position affect the docking scores, the presence of rhamnose or a rutinoside moiety in C-3 position enhances the bioactivity of the selected compounds which is in agreement with the results of Owis et al. (2020). Moreover, the presence of a glucoside group in flavonol structures increases the possibility of hydrogen bonds creation compared to the rhamnoside unit. According to the docking study of Jo and his collaborators (2019), quercetin-3-*O*-β-*D*-glucoside, which is a homolog of quercitrin where rhamnoside is substituted by glucoside, showed that the hydroxymethylene group (CH_2–OH) of the glucoside moiety creates a supplementary hydrogen bond with Glu169 that contributes to its closer binding to the S_1 subunit than the rhamnoside moiety of quercitrin. Moreover, the substitution of the flavonol with additional hydroxyl groups especially in A ring creates more interactions between the docked sites and the tested molecules. This was clearly observed in the study of Jo et al. (2020) which tested the ability to inhibit SARS-CoV $3CL^{pro}$ of 64 molecules belonging to ten different classes of flavonoids. According to this finding, flavonols were the most active compounds compared to the other classes of flavonoids. Indeed, morin, kaempferol and herbacetin bind with the MERS-CoV 3C-like protease. However, herbacetin which is a kaempferol derivative with an additional hydroxyl group at C-8 position had the strongest binding affinity compared to the other tested molecules. This molecule occupies the S_1 and S_2 sites of MERS-CoV 3CLpro and forms four hydrogen bonds. However, the main bond strengths were occurred between the C-8 position with Glu166, Gln189 and His41 (Jo et al., 2019, 2020) (Fig. 2.).

Previous studies reported that rutin exhibited a high stability compared to many other flavonols namely narcissin, calendoflaside (isorhamnetin-3-*O*-rhamnosyl-rhamnose), calendoflavoside (isorhamnetin-3-*O*-neohesperidoside), quercitrin, isoquercitrin and isorhamnetin (Das et al., 2020; Owis et al., 2020). The reactivity of rutin is due to the presence of rutinoside moiety and four free hydroxyl groups on the aglycone skeleton. While the substitution of rutin with a methoxy group in C-3′ of B ring to obtain narcissin reduces the reactivity of this molecule which is previously reported by Owis et al. (2020). In contrast, the presence of a glucose unit in the flavonol skeleton gives a strong binding affinity compared to the rhamnose unit as in the case of isoquercitrin and quercitrin (Jo et al., 2019). Also, the position and the type of branched osidic units may affect the binding energy. The comparison between the structures of isorhamnetin derivatives (narcissin and calendoflavoside) could explain this suggestion. In fact, these molecules bear the same branched osidic units (glucose-rhamnose) on the C-3 position of the isorhamnetin skeleton. However, the linkage between the

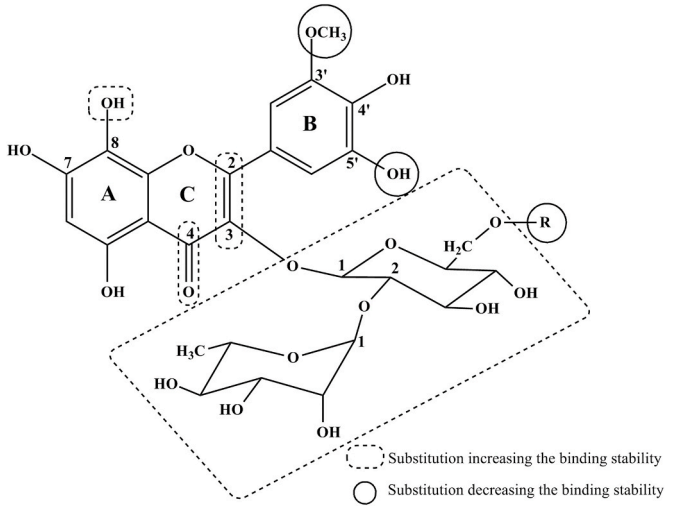

Fig. 2. Substitutions affecting the binding stability of flavonols to the $3CL^{pro}$.

osidic units differ for narcissin (-β-D-Glc-(1 → 6)-α-L-Rha) and for calendoflavoside (-β-D-Glc-(1 → 2)-α-L-Rha). This could increase the steric hindrance in the structure of calendoflavoside and decreases the capacity of hydrogen bonds as well as the formation of electrostatic interactions (Fig. 3).

According to the study of Qamar et al. (2020), performed on 32,297 molecules with potential antiviral activities used in traditional Chinese medicine, two flavonols namely myricitrine and myricetin-3-*O*-β-D-glucopyranoside have been docked for their potential anti-COVID-19 capacity against SARS-CoV-2 $3CL^{pro}$. The obtained results were compared with nelfinavir, prulifloxacin and colistin as positive controls. The data showed that these compounds had a strong ability to bind with the receptor-binding site and catalytic dyad (Cys-145 and His-41) of SARS-CoV-2 $3CL^{pro}$ with high docking scores, high binding affinity and close interactions with the conserved catalytic dyad residues. Indeed, these compounds are also non-toxic, biologically active and naturally found in many medicinal species. In addition, the ability of many flavonols namely astragalin, kaempferol, quercetin, quercetin-3-*O*-glucoside and quercitrin to interact with SARS-CoV-2 proteins ($3CL^{pro}$, PL^{pro}) was studied. The data indicated that all the tested molecules have consistent interactions and possess very good binding affinities to all the viral proteins compared to remdesivir as positive control. The highest docking score was observed in quercetin-3-*O*-glucoside, which binds to His74, Arg83, Tyr155, Asn157, His176 amino acid residues of viral protein at the binding pocket of PL^{pro} with eight hydrogen bonds (Hiremath et al., 2020). Also, quercetin derivatives including quercetin-3-vicianoside, quercetin-3-glucuronide-7-glucoside and quercetin-7-*O*-galactoside gave low binding energy with M^{pro} target (Joshi et al., 2020). Further, Chen et al. (2006) reported that quercetin-3-*O*-β-galactoside bound to SARS-CoV $3CL^{pro}$ with the Gln189 residue playing a key role in stabilizing binding. In the paper of (Bhatia, 2020) and his collaborators, kaempferol-3-*O*-glucuronide showed a high docking score (−9.8 kcal/mol), which could be explained by the presence of hydroxyl groups, acid and ketone functions, able to promote hydrogen bonds and Van Der Waal interactions. According to the study of Da Silva et al. (2020), all glucuronide and sulfate derivatives of quercetin and kaempferol interact better than their aglycones (quercetin and kaempferol) to the $3CL^{pro}$.

Among ten polyphenolic compounds papyriflavonol A (prenylated flavonol) was the most potent inhibitor of PL^{pro} (Park et al., 2017). In addition, many researches indicated that quercetin and its derivatives such as herbacetin, myricetin, morin, rutin, kaempferol and its derivatives are able to form stable complexes with M^{pro} and to record good binding affinities scores (Ranjan et al., 2020; Huynh et al., 2020; Tallei et al., 2020; Islam et al., 2020; Mahmud et al., 2020; Swain et al., 2020; Lingwan et al., 2020; Sekiou et al., 2020; Rehman et al., 2020; Mishra et al., 2020; Khaerunnisa et al., 2020).

4.3. Flavonols targeting the S protein and ACE2 receptor

The S protein is a homotrimeric glycoprotein located on the surface of the SARS-CoV-2 virion which plays multifunctional roles in the COVID-19 viral infection transmission including host receptor binding, cell tropism, and pathogenesis (Sigrist et al., 2020). The S protein is also the major target for the host immune system. According to Martin and Cheng (2020), these proteins are considered as virulence determinants and powerful immunogenic molecules able to solicit the humoral immune response and considered as interesting epitopes for vaccine development and antibody-based therapeutic interventions (Lv et al., 2020). The S protein is a crucial recognition factor for virus attachment and entry to the host cells. In fact, the interaction with a high affinity and mutability between the receptor-binding domain (RBD) located on the S1 subunit of the S protein and the ACE2 receptor undergoes several structural rearrangements and conformational changes in the S protein inducing the exposure of a proteolytic site. This latter is cleaved by the host cellular serine protease TMPRSS27 leading to the dissociation of the

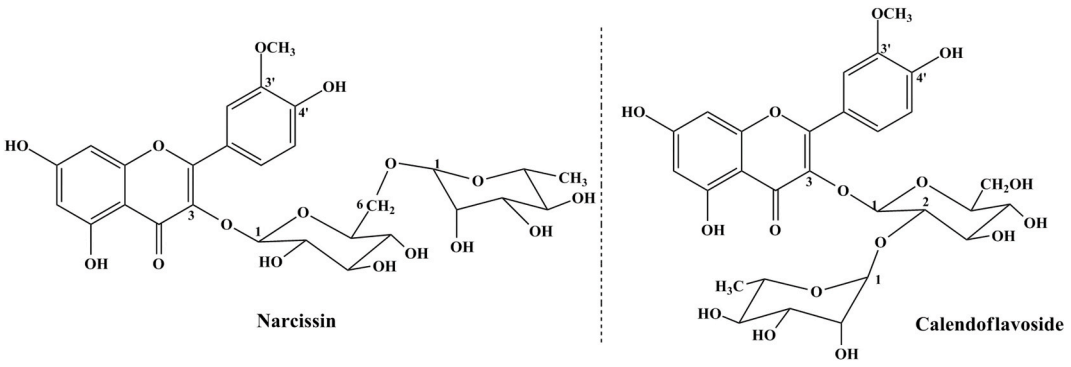

Fig. 3. Structures of narcissin and calendoflavoside.

S1 subunit and the transition from the S2 subunit to a postfusion state which allows the endocytosis of the virus (Letko et al., 2020; Walls et al., 2020). For this, molecules able to disturb and destabilize the binding between SARS-CoV-2 spike protein and ACE2 receptor leading to the inhibition of membrane fusion and the viral nucleocapsid transfer could constitute effective drugs able to block the viral host cell attachment and endocytosis (Bongini et al., 2020).

Many studies reported the ability of flavonols to bind with SARS-CoV-2 spike protein and ACE2 receptor. Indeed, this ability to interact with these proteins is highly related to the chemical structures of these molecules. The existence of ortho di-OH hydroxyl groups in the B ring of flavonols creates a stable complex reinforced by strong hydrogen bonds between S protein and the flavonols (Fig. 4A). This finding was confirmed by the paper of Pandey and his colleagues (2020), which reported the docking study of four flavonols namely fisetin, quercetin, isorhamnetin and kaempferol against S protein. Data showed that these compounds interacted with the S2 domain of the S protein with high binding affinities compared to hydroxychloroquine as a positive control. The comparison between the results of quercetin and its derivative isorhamnetin having a methoxyl group (OMe) attached at the C-3′ position of the B ring, revealed that steric hindrance of the OMe groupment reduces the formation ability of hydrogen bonds and affects the nature of the interactive residues (Fig. 4B). In addition, the absence of hydroxyl group in C-3′ position reduces the capacity of hydrogen bonds formation (Fig. 4C).

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 conformational changes and viral entry inhibition (Ngwa et al., 2020; Vijayakumar et al., 2020). According to the investigation of Pandey et al. (2021) galangin, morin and myricetin exhibited good docking scores against spike glycoprotein in comparison with abacavir and hydroxychloroquine as standard drugs. In addition, according to the study of Tallei and his collaborators (2020) herbacetin, kaempferol and morin revealed a good ability to bind with S protein. Quercetin had a very strong ability to interact with to ACE2 receptor better than hydroxychloroquine and many other antiviral drugs, and possessed good binding interactions with S protein (Sekiou et al., 2020; Pandit and Latha, 2020; Kiran et al., 2020; Vijayakumar et al., 2020; Lingwan et al., 2020). Also, quercetin-*O*-pentoside, quercetin-*O*-rhamnoside, kaempferol-*O*-pentoside and kaempferol showed strong binding affinity with the human ACE2 receptor. In fact, quercetin-*O*-pentoside presents a high binding affinity compared to kaempferol-*O*-pentoside, which indicates the important role of hydroxyl groups in the occurrence of hydrogen bonds (Lingwan et al., 2020). Joshi and his collaborators (2020) reported that quercetin derivatives (quercetin-3-*O*-vicianoside, quercetin-3-*O*-glucuronide-7-*O*-glucoside and quercetin-7-*O*-galactoside) possess high binding scores with the ACE2 receptor compared to the reference molecule (Joshi et al., 2020). In addition, according to the paper of Balmeh et al. (2020), quercetin-3-*O*-rutinose (Rutin) had a strong binding affinity to the TMPRSS2. This enzyme is involved in proteolytic cleavage of the S1/S2 junction of the ACE2 receptor leading to viral endocytosis.

4.4. *Flavonols targeting the RdRp*

RdRp also known as nsp12 is a central component of SARS-CoV-2 replication/transcription machinery. With the assistance of nsp7 and nsp8 as co-factors, this enzyme catalyzes the synthesis of viral RNA and plays a central role in the replication and transcription process. Indeed, this latter constitutes a primary target for docking studies, and molecules able to disturb its activity may be considered as potential treatments of COVID-19 viral infection (Gao et al., 2020; Yu et al., 2020).

Quercetin, kaempferol, and some of their glucuronide and sulfate derivatives were tested against SARS-CoV-2 RdRp using molecular docking (Da Silva et al., 2020). The obtained data indicated that quercetin and kaempferol, as well as their glucuronide and sulfate

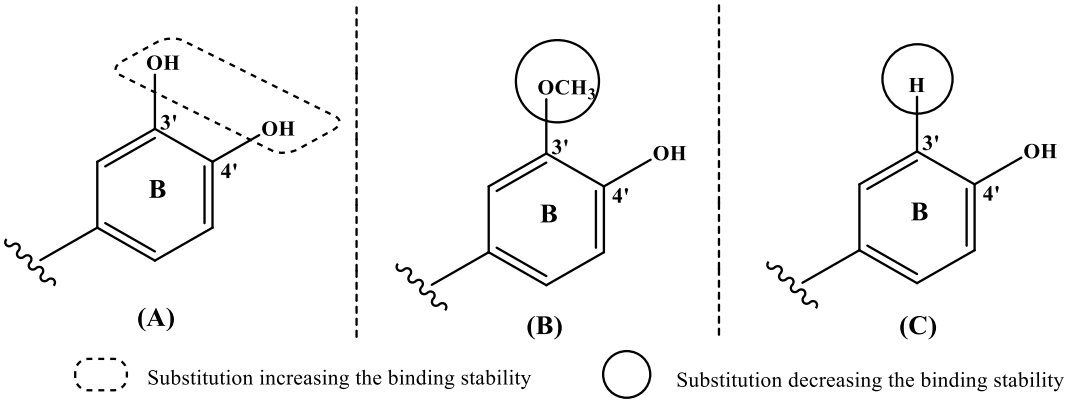

Fig. 4. Effects of the substitution of C-3' (B ring) on the binding stability of flavonols to the S protein.

derivatives, interact as potential inhibitors for RdRp protein. The comparison between the values of binding energies revealed that most of quercetin derivatives (quercetin-3-*O*-rutinose, quercetin-7-*O*-glucuronide, quercetin-3′-*O*-glucuronide, quercetin-3-*O*-glucuronide, quercetin-7-*O*-sulfate, quercetin-3′-*O*-sulfate) except quercetin-3-*O*-sulfate possess binding affinities better than quercetin itself. Quercetin-3-*O*-rutinose (rutin) was the most active compared to all quercetin derivatives, which confirms the importance of the rutinoside moiety to increase the number of hydrogen bonds and electrostatic interactions. Also, this study reported that molecules substituted with glucuronic units had low binding energies to the RdRp. The reactivity of the glucuronic units could be attributed to the presence of the hydroxyl groups and carboxylic function. The attachment position of glucuronic unit with quercetin had effects on its reactivity. According to these results, the substitution of quercetin with a glucuronic unit in C-3 position reduces its reactivity compared to the substitution in C-7 and C-3′ positions. The data indicated that glucuronide derivatives of kaempferol are more active than their sulfate derivatives. Kaempferol-3-*O*-rutinose (nicotiflorin) had the strongest activity compared to all the tested molecules in this study. Also, the substitution with a sulfate unit at C-3 of both aglycones (kaempferol and quercetin) reduces their reactivity.

Fisetin, quercetin and hyperoside displayed high affinities with the RNA-polymerase active site, and the nidovirus RdRp-associated nucleotidyltransferase-fingers site (NiRAN) compared to remdesivir as the control drug. Indeed, hyperoside forms the maximum possible number of non-covalent interactions with RNA-polymerase site due to the presence of galactose moiety. Moreover, fisetin with the absence of a hydroxyl group in C-5 position of B ring showed a strong binding affinity than that of quercetin for the RNA polymerase NiRAN-fingers site. This could be explained by the absence of chelating bonds between the ketone function in C-4 position and OH group in C-5, which liberate the free doublets of the ketone function leading to the formation of more hydrogen and electrostatic bonds (De Jesús-González et al., 2020). Furthermore, flavonols such as afzelin, biorobin, myricitrin, astragalin, kaempferol, quercetin, quercetin-3-*O*-glucoside and quercitrin showed strong binding affinity to RdRp (Hiremath et al., 2020; Vijayakumar et al., 2020).

5. Safety and protective effects of flavonols

Many clinical studies confirmed the safety of quercetin as a supplement and supported its addition to the dietary diet. This molecule was added as a supplemental ingredient to the Food and Drug Administration's Generally Recognized as Safe list (GRAS) (Dabeek and Marra, 2019). The study of (Harwood, 2007) and his collaborators reviewed the genotoxic and mutagenic effects of quercetin on several animal and human models. The results confirm the safety of quercetin and the absence of *in vivo* toxicity and carcinogenic effects. Quercetin had interesting protective effects due to its large spectrum of biological activities. This secondary metabolite limits the cardiotoxic effects of bisphenol-A (Vanani et al., 2020) and prevents the hepatotoxicity induced by paracetamol, 5-fluorouracil, sodium fluoride, and thioacetamide in rats (El Faras and Elsawaf, 2017; Gelen et al., 2017; Nabavi et al., 2012; De David et al., 2011). Moreover, this molecule is potentially effective for the treatment of chronic kidney disease due to its antioxidant, diuretic and nephroprotective activities (Shebeko et al., 2018). Additionally, quercetin exerts a significant protective action against the reproductive toxicity induced in several models (Aziz et al., 2018; Mi et al., 2010; Farombi et al., 2012). Rutin had no acute or chronic toxicity (Wilson et al., 1947). Indeed, this molecule was reported to assess many protective effects on several vital organs. It had protective effects against CCl_4-induced hepatotoxicity, nephrotoxicity, and reproductive toxicity due to its antioxidant and antidyslipidemic activities (Elsawy et al., 2019). The pretreatment with rutin significantly attenuated pirarubicin-induced cardiotoxicity in rats (Wang et al., 2018), blood toxicity and fluoride-induced oxidative stress-mediated cardiotoxicity (Umarani et al., 2015). Jahan and his collaborators (2018), reported that the cotreatment with rutin ameliorates the infertility of animals and reduces testicular toxicity signs (Jahan et al., 2018). Also, rutin was reported to attenuate intestinal toxicity induced by methotrexate due to its significant anti-inflammatory, antioxidant and antiulcer properties (Gautam et al., 2016). Quercetin and rutin had cardioprotective effects in ischemia-reperfusion-induced myocardial infarction in both normal and diabetic rats (Annapurna et al., 2009). Rutin had many kidney protective activities tested in several models including oxonate-induced hyperuricemia and potassium bromate-induced nephrotoxicity and possess protective effects on lung tissue in cases of acute lung injury by the prevention of polymorphonuclear granulocytes infiltration in bronchoalveolar lavage fluid and the reduction of the inflammatory response (Ganeshpurkar et al., 2017). Myricetin was found to be non-toxic in several *in vivo* models (Semwal et al., 2016). This molecule had a protective effect against tert-butylhydroperoxide (t-BHP) induced oxidative stress in human erythrocytes (Pandey et al., 2009) and possessed antigenotoxic and hepatoprotective properties against pyrogallol-induced toxicity in mice (Matić et al., 2013). The pretreatment with myricetin notably reduced the cisplatin-induced nephrotoxicity in mice (Hassan et al., 2017). Myricetin protects cardiomyocytes against inflammatory injury and possesses cardioprotective, anti-hypertensive, antihyperglycemic, and antihyperlipidemic effects (Qiu et al., 2017; Sun et al., 2019; Wang et al., 2019). There are controversial reports regarding the safety of kaempferol. Indeed, various *in vitro* studies demonstrated the genotoxic and the carcinogenic effects of kaempferol. However, it is supposed that the low oral bioavailability of kaempferol prevents it *in vivo* toxicity (Devi et al., 2015; Calderon-Montano et al., 2011). In addition, no human or animal trials reported the potential toxicity of kaempferol (Dabeek and Marra, 2019). However, this metabolite attenuates nephrotoxicity and prevent renal injury induced by mercuric chloride (Vijayaprakash et al., 2013) and had significant *in vivo* protective effects on hepatotoxicity induced by alcohol and drugs (Isoniazid and Rifampicin) (Wang et al., 2015a; Shih et al., 2013). Kaempferol derivatives like kaempferol-3-*O*-rutinoside and kaempferol-3-*O*-glucoside possess hepatoprotective effects against CCl_4-induced oxidative liver damage (Wang et al., 2015b). Several *in vitro* and *in vivo* studies documented the cardioprotective effects of kaempferol (Dabeek and Marra, 2019). Furthermore, kaempferol protects pancreatic beta cells from 2-deoxy-*D*-ribose-induced oxidative damage through the attenuation of lipid peroxidation inducing the decrease of type II diabetes progression (Lee et al., 2010).

Isorhamnetin derivatives were revealed to be non-toxic towards several cell lines (Ressaissi et al., 2017). Isorhamnetin possesses many *in vitro* and *in vivo* anti-pulmonary fibrosis effects and hepatoprotective activities (Gong et al., 2020). The pretreatment with isorhamnetin reduces significantly the Doxorubicin-induced chronic cardiotoxicity (Sun et al., 2013). Also, this molecule had neuroprotective (Gong et al., 2020; Li et al., 2016) and renoprotective properties (Qiu et al., 2016). Morin subchronic toxicity was studied *in vivo* on both sexes of F344 rats and the no-observed-adverse-effect level was estimated. During 13 weeks of the treatment, no mortalities or abnormal clinical signs were observed. However, the treatment induces a significant increase in several biochemical parameters (Cho et al., 2006). Morin had *in vivo* hepatoprotective and nephroprotective effects on doxorubicin-induced hepatorenal toxicity (Kuzu et al., 2019). In addition, this molecule displays cardioprotective and neuroprotective activities (Verma et al., 2019; Liu et al., 2018; Ma et al., 2017). Long-term feeding of fisetin to mice was safe, no toxic signs were observed at doses up to 2 g/kg. Also, no histological modifications were observed in multiple tissues (lungs, spleen, liver, kidneys, heart, stomach, intestine, testes, and ovary) (Pal et al., 2016). Fisetin possesses interesting protective effects on acetaminophen-induced hepatotoxicity *in vitro* and *in vivo* (Zhao et al., 2019) and protects the liver from binge alcohol-induced toxicity (Koneru et al., 2016). This molecule has neuroprotective effects and protects against myocardial ischemia/reperfusion injury (Fazel Nabavi

and Braidy, 2016; Long et al., 2020). Also, fisetin supplementation improves insulin resistance and inflammatory response against metabolic stress-inducing renal injury (Ge et al., 2019).

6. Bioavailability limitations of flavonols

The use of flavonol glycosides as future drugs had some inconvenience. The presence of sugar moieties usually increases the bioavailability of flavonoid aglycone. But in some cases, the nature of the substituted sugar affects the digestibility and the absorbability of these natural compounds. Indeed, flavonols with glucose moieties are absorbed more rapidly than flavonoids with rhamnosides, rhamnoglucosides, rutinosides and neohesperidosides substitutions (Xiao, 2017). Glucose moieties are easily hydrolyzed in the small intestine epithelial cells. However, the lack of α- L -rhamnosidase or rutinosidase in human cells makes the bioavailability of relative flavonoids largely dependent on their hydrolysis by intestinal bacteria (Bang et al., 2015). Furthermore, few intestinal bacterial strains can achieve cleavage of these types of bonds (Amaretti et al., 2015), but the tested molecules could be active even after the cleavage of the glycosidic part by hydrolyzing enzymes in the human gastrointestinal tract because the bioavailability of the molecules is due to the aglycone part (Valentová et al., 2014). However, the use of smart drug delivery technologies such as polymeric nanoparticles/microspheres, inorganic nanoparticles, phospholipid vesicles, inclusion complex, micelles and other nanomaterials may increase the absorbability, reduce the bioavailability limitations and improve the therapeutic effects (Wang et al., 2020b; Oueslati et al., 2020).

7. Conclusion

The evidence reviewed in the present study based on recent computational and experimental investigations indicated that flavonoids and especially flavonols class may constitute a promising therapeutic strategy against COVID-19. Indeed, flavonols have the ability to disturb and destabilize the binding between S protein and ACE2 receptor leading to the inhibition of virus entry and able to halt the activity of several enzymes involved in the replication cycle of the virus including $3CL^{pro}$, PL^{pro} and RdRp. Due to their large spectrum of biological activities, these molecules may alleviate the severity of COVID-19 symptoms and modulate the immune response.

CRediT authorship contribution statement

Chaima Mouffouk: Writing - original draft, Conceptualization, Methodology, Preliminary research and Manuscript revision. **Soumia Mouffouk:** Writing - original draft, Figures preparation, Writing - review & editing. **Sara Mouffouk:** Writing - review & editing. **Leila Hambaba:** Supervision. **Hamada Haba:** Supervision.

Declaration of competing interest

None.

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