Review

**In silico** evaluation of *Vitis amurensis* Rupr. Polyphenol compounds for their inhibition potency against COVID-19 main enzymes Mⁿpro and RdRp

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**Abstract**

The rapid transmission of the pneumonia (COVID-19) emerged as an entire worldwide health concern and it was declared as pandemic by the World Health Organization (WHO) as a consequence of the increasing reported infections number. COVID-19 disease is caused by the novel SARS-CoV-2 virus, and unfortunately no drugs are currently approved against this disease. Accordingly, it is of utmost importance to review the possible therapeutic effects of naturally-occuring compounds that showed approved antiviral activities. The molecular docking approach offers a rapid prediction of a possible inhibition of the main enzymes Mⁿpro and RdRp that play crucial role in the SARS-CoV-2 replication and transcription. In the present work, we review the anti-viral activities of polyphenol compounds (phenolic acids, flavonoids and stilbene) derived from the traditional Chinese medicinal *Vitis amurensis*. Recent molecular docking studies reported the possible binding of these polyphenols on SARS-CoV-2 enzymes Mⁿpro and RdRp active sites and showed interesting inhibitory effects. This antiviral activity was explained by the structure-activity relationships of the studied compounds. Also, pharmacokinetic analysis of the studied molecules is simulated in the present work. Among the studied polyphenol compounds, only five, namely caffeic acid, ferulic acid, quercetin, naringenin and catechin have drug-likeness characteristics. These five polyphenols derived from *Vitis amurensis* are promising drug candidates for the COVID-19 treatment.

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1. Introduction

The Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection was detected for the first time in December 2019 at Wuhan, China (Zhu et al. 2020). Then, SARS-CoV-2 (COVID-19) was emerged as a pandemic. As of February 1st, 2022, more than 373.229 million cases and 5.658 million deaths were reported (www.who.int). SARS-CoV-2 disease is characterized by several symptoms such as dry cough, fever, headache, breath shortness, sore throat, production of sputum, muscle pain, joint pain, fatigue, loss of taste and smell as well as pneumonia. When multiple organs, mainly respiratory ones fail, the death occurs (WHO 2020). The transmission of the COVID-19 is essentially due to the lack of approved drugs, which lead to a large increase in the number of untreatable infections that collapse the world healthcare system.

Drug repurposing, also known as drug reprofiling, repositioning or re-tasking, is a strategy for identifying new uses for drugs that are outside the scope of the initial medical indication (Ashburn and Thor 2004). This strategy suggested different anti-viral drugs to cure COVID-19 patients (Muralidharan et al. 2021). However, it should be noted that a specific drug needs to be approved for treating COVID-19 patients. Newly synthesized molecules were also tested for their potential inhibition of SARS-CoV-2 viral genome replication and transcription (Bhardwaj et al. 2021).

Traditional herbal medicines are natural reservoir of molecules with anti-viral properties (Huang et al. 2020; Ghosh et al. 2021a). Considering the growing threat of COVID-19 pandemic, it is essential to study the efficacy of such molecules against SARS-CoV-2. Polyphenols are a group of natural compounds that showed anti-viral properties against RNA viruses (Wohlfarth and Efferth 2009; Özçelik et al. 2011; Rojas et al. 2016; Weng et al. 2019). Nowadays, such polyphenol compounds were in silico screened for their SARS-CoV-2 proteases inhibition (da Silva et al. 2020; Huang et al. 2020; kaviarasu et al. 2020).

In the present work, we aimed to summarize the structure, the pathogenesis and the main enzymes of the SARS-CoV-2 and to evaluate the polyphenol compounds derived from the Chinese therapeutic Vitis amurensis that may be used as promising drug candidates in the COVID-19 therapy.

2. Structure and pathogenesis of the SARS-CoV-2

SARS-CoV-2 is a single-stranded positive-sense enveloped RNA that belongs to the β-corona virus subgroup with a genome of about 30 Kb (Wu et al. 2020a). SARS-CoV-2 has a typical genomic organization which is 5’ untranslated region (UTR), open reading frame (ORFs) and genes encoded for spike (S), envelope (E), membrane (M) and nucleocapside (N) (Wu et al. 2020a) (Fig. 1). ORF 1a and ORF 1b encode for two overlapping polyproteins pp1a and pp1ab which are further processed by viral-encoded proteases into 16 non specific proteins (nsp) essential for the replication and the transcription of the virus (Paraskevis et al. 2020).

SARS-CoV-2 also has a hemagglutinin-esterase glycoprotein that makes it different from other coronaviruses (Khailany et al. 2020).

The SARS-CoV-2 infection is initiated by S protein-host cell receptor interaction. The host cell serine proteases TMPRSS2 cleave the viral S protein into two subunits S1 and S2, which are responsible for the cell recognition and the membrane fusion (Wallis et al. 2020). The S1 C-terminal domain binds to the host cell receptor Angiotensin-Converting Enzyme 2 (ACE2). As a result, a conformational change of the S2 subunit occurs allowing the release of the virus in the host cell cytoplasm then the viral RNA starts to express (Zhou et al. 2020). The viral genome starts translation into the viral polyproteins using the the host cell translation machinery (Fig. 2).
3. SARS-CoV-2 main enzymes

3.1. Chymotrypsin-like protease (Mpro)

Chymotrypsin-like 3CLpro, also named Mpro and nsp5, is a cysteine protease. It is an important enzyme found in coronaviruses that has proteolytic function in the maturation stage of the virus. It cleaves at least 11 sites on polyprotein-1a (pp1a) and polyprotein-1ab (pp1ab) found in the viral genome to cut nsp4-nsp16 allowing the formation of several non-structural proteins such as RNA dependant RNA polymerase, helicase, endonuclease and 2'-O-methyltransferase (2’-O-Mtase) (Hegyi et al. 2002).

Jin et al. (2020) showed that SARS-CoV-2 Mpro is composed of three domains: (i) domain I contains the residues from 8 to 101, (ii) domain II contains residues from 102 to 184. Both domains I and II have an antiparallel β-barrel structure, (iii) domain III contains residues from 201 to 303 with five α-helices arranged into a largely antiparallel globular cluster. Domain III is linked to domain II by a long loop region (residues 185–200). The SARS-CoV-2 Mpro (PDB ID: 6LU7) active site is composed of Thr24, Thr25, Thr26, Leu27, His41, Thr45, Met49, Leu141, Asn142, Gly143, Ser144, Cys145, His163, Met165, Glu166 and His172 (Fig. 3). The Mpro His41-Cys145 dyad is responsible for the catalytic activity of the SARS-CoV-2. His41-Cys145 is the most important target for drugs against coronaviruses (Wu et al. 2020b).

The inhibition of the catalytic dyad activity ultimately helps in the inhibition of the main protease activity (Jin et al. 2020). In fact, the inhibition of Mpro arrests the virus multiplication inside the host cell by blocking essential processes such as viral genome replication and transcription. The sequence of the Mpro is highly conserved through coronavirus species. This similarity exceed 96% when compared Mpro from SARS-CoV-2, SARS-CoV and MERS (Ghosh et al. 2021a). This makes Mpro an ideal target for broad-spectrum anti-CoV therapy.

3.2. RNA dependant RNA polymerase (RdRp)

RNA dependant RNA polymerase (RdRp), also known as nsp12, is a non-structural protein formed through the cleavage of the polyproteins by Mpro. RdRp is a crucial enzyme and plays an important role in both the replication and the transcription of the virus RNA (Malik et al. 2020). The RdRp expresses a minimal activity on its own, but the complexation with the co-factors nsp7 and nsp8 significantly stimulates its polymerase activity (Subissi et al. 2014). The COVID-19 virus RdRp (PDB ID: 6NUR) active site is shown in Fig. 3. It consists of seven conserved motifs A-G. The motif C (residues Phe753 to Asn767) contains the catalytic residues (Ser759-Asp760-Asp761) which are important for the catalytic activity of the RdRp protease (Jiang et al. 2021). RdRp is a fundamental target for the treatment against COVID-19 since it provides a possible strategy against viral replication (Wu et al. 2020b). It is of outmost importance to note that RdRp enzymes in coronaviruses are remarkably similar. In fact, the SARS-CoV RdRp exhibits ~ 97% sequence similarity with that of SARS-CoV-2 (Singh et al. 2020). It is also important to mention that there is no human polymerase counterpart that resembles the sequence/structural homology with coronaviruses RdRp (Borgio et al. 2020). Accordingly, the development of RdRp inhibitors would be potential therapeutic strategy with no risk of crosstalk with human polymerases.
4. Botanical description and therapeutic uses of *Vitis amurensis*

*Vitis amurensis* is a wild grape species of Vitaceae family. The leaves have light green color and an alternate arrangement (Peng et al. 2001). The branches are spread and can reach 15 m long in the whole growth. *Vitis amurensis* is generally dioecious species. However, few forms of hermaphroditic flowers were reported in the literature (Peng et al. 2001). In dioecious *Vitis amurensis*, male vines produce only functionally male flowers and no mature berries are available (Shen et al. 2018). The flower buds start to differentiate from August to September (Peng et al. 2001). The berries are small and round with a diameter ranging from 5 to 12 mm (Liu and Li 2013). They have fine taste and 2 to 4 seeds (Peng et al. 2001).

*Vitis amurensis* is resistant to the abiotic and biotic stresses (Huang and Lin 1999; Song et al. 2008). For that reason, it is often used to breed new cultivars tolerant/resistant to cold and diseases. *Vitis amurensis* has high medicinal values. It was listed in the Korean herbal Pharmacopoeia (1987) for the treatment of stroke and the stimulation of memory improvement. The Chinese med-
icine used the *Vitis amurensis* leaves, stems and roots to treat pains resulting from abdominal complaints, stomachache and neuralgic cancer (Huang and Lin 1999). *Vitis amurensis* berries are often given to the consumers as a rich source of soluble sugars (glucose and fructose), proteins, vitamins and secondary metabolites (Zhang and Li 2000). It was found that polyphenols extracted from *Vitis amurensis* stems exhibit potential neuraminidase inhibitory activity (Nguyen et al. 2012). Chen et al. (2018) showed that *Vitis amurensis* leaf, stem and berry are beneficial as food supplement against influenza virus (IAV) subtype H1N1. However, as far as the authors are aware, the anti-viral activity of *Vitis amurensis* has not been fully analyzed and whether it can exhibit any anti-SARS-CoV-2 activity by inhibiting the proteolytic activity of Mpro and RdRp is not yet discussed. The present work fulfills the progress on polyphenol studies of *Vitis amurensis* over the past decades and lists their inhibitory potency against SARS-CoV-2 Mpro and RdRp with the aid of in silico docking results.

![Chemical structure of the studied *Vitis amurensis* polyphenols](image)

**Fig. 4.** Chemical structure of the studied *Vitis amurensis* polyphenols [molecules are drawn with ChemDraw 20.0]
5. Phenolic phytochemicals in *Vitis amurensis*

*Vitis* spp. polyphenols show an increasing interest for their nutraceutical, pharmacological, and cosmetic benefits (Dani et al. 2010). Phytochemical studies revealed the presence of 140 phenolic compounds among which phenolic acids, flavonoids and stilbenes in *Vitis amurensis* (Huang and Lin 1999; Wang et al. 2000; Ha et al. 2009; Zhao et al. 2011; De la Cruz et al. 2012; Ji et al. 2015). Phenolic acids are divided into two main groups hydroxybenzoic acids with 7 carbon atoms (C6-C1) (e.g. gallic acid) and hydroxycinnamic acids with 9 carbon atoms (C6-C3) (e.g. caffeic acid, ferulic acid and chlorogenic acid) (Silva et al. 2019). Flavonoids form a group of diverse compounds that share a common diphenylpropane skeleton formed by 2 benzene rings connected by a linear three-carbon chain (C6-C3-C6). Flavonoids have, commonly, three OH groups, two of which are located in the ring A (at 5 and 7 positions) and one is located in the 3’ position of the ring B. Flavonoids can be found as free or bounded to glucose, galactose, rhamnose or xylose to form glycosides (Majewska-Wierzbicka and Czeczot 2012). The main flavonoid subclasses found in *Vitis amurensis* include flavonols (e.g. quercetin, kaempferol and myricetin), flavonones (e.g. naringenin), flavon-3-ols (e.g. catechin, epicatechines and epigallocatechin gallate), flavones (e.g. luteolin) and anthocyanins (e.g. cyanidin and peonidin). Stilbenes constitute a small group of polyphenolic compounds characterized by a (C6-C2-C6) 1,2-diphenylethylene skeleton (Chong et al. 2009) and most plant stilbenes are trans-resveratrol (3,5,4’-trihydroxy-trans-stilbene) derivatives. In *Vitis amurensis* up to 92 stilbene compounds were isolated and most of them are dimers, trimers, tetramers and pentamers (Shen et al. 2017).

6. *Vitis amurensis* polyphenols with the potential to inhibit COVID-19

The structures of the studied polyphenol compounds are shown in Fig. 4 and their anti-viral activities were tested (Table 1). These natural secondary metabolites include phenolic acids, flavonoids and a stilbene.

### 6.1. Phenolic acids

Phenolic acids are polyphenolic compounds present mainly in *Vitis amurensis* berry and grape skin (Zhao et al. 2011; Ji et al. 2015). Gallic acid (1) is a simple hydroxybenzoic acid that is found as free form in *Vitis amurensis* grape skin (Ji et al. 2015; Chen et al. 2018). It has a potent antiviral effect. For example, it has a strong anti-HCoV-NL63 (Human coronavirus NL63) potential (Weng et al. 2019). Compound 1 showed also an anti-IAV (You et al. 2018) as well as an anti-parainfluenza type 3 virus (HPIV3) and an anti-herpes virus type 1 (HSV-1) potency (Özçelik et al. 2011).

**Table 1**

| Compound | Part of the plant | Virus | References |
|----------|------------------|------|-----------|
| 1        | Grape skin       | HCoV-NL63, IAV, HPIV3, HSV-1 | Weng et al. 2019, You et al. 2018, Özçelik et al. 2011 |
| 2        | Berry            | HRV5, HBV, HCV | Park et al. 2014, Wohlfarth and Efferth 2009 |
| 3        | Berry            | HCoV-NL63, HBV, HPIV3, Influenza, HIV | Zhang et al. 2020, Wang et al. 2009, Özçelik et al. 2011, Maruta and He, 2020 |
| 4        | Grape skin       | MHV, HSV, ADV-11, EV71, IAV, PPV | Liu et al. 2016, Sheng et al. 2008 |
| 5        | Grape skin       | SARS-CoV, IAV, HCV, EV71, HIV, HBV | Nguyen et al. 2012, Liu et al. 2016, Rojas et al. 2016, Yao et al. 2018 |
| 6        | Root             | SARS-CoV, IAV, HCV, EV71, HIV, HBV | Lee et al. 2003, Fan et al. 2011, Nosrati et al. 2018 |
| 9        | Grape skin       | IAV(H1N1 and H9N1), SARS-CoV, HIV, MULV, M-MULV | Jeong et al. 2009, Yu et al. 2012, Ono et al. 1990, Ono et al. 1990 |
| 11       | Berry            | HCV, DENV-2, CHIKV | Khachatourian et al. 2012, Frabasile et al. 2017, Ahmadi et al. 2016 |
| 12       | Berry, Grape skin | IAV, HSV-1, HBV, HPIV, HCV, DENV, PRRSV, EBOV, HIV, IAV | You et al. 2018, Colpitts et al. 2014, He et al. 2011, He et al. 2013, Colpitts et al. 2014, Raekiansyah et al. 2018, Zhao et al. 2014, Reid et al. 2014, Li et al. 2011, Colpitts et al. 2014 |
| 16       | Berry, leaf      | SARS-CoV, HCV, HIV | Zhuang et al. 2009, Lee et al. 2019, Pflieger et al. 2013 |
A virtual molecular docking study investigating commercial drugs inhibition of SARS-CoV-2 M^pro~(PDB ID: 6LU7) showed that compound 1 induces hydrogen bonding with the amino acid residues Leu141, Gly143, Ser144, His163 and Glu166 with a binding energy of −4.5 Kcal/mol (Arokiyaraj et al. 2020) which makes it a potential inhibitor of SARS-CoV-2 M^pro (Table 2). Compound 1 has several potential therapeutic properties including antioxidant, anticancer and antimicrobial (Ow and Stupans 2003, Yilmaz and Toledo 2004). Furthermore, 1 possesses an anti-inflammatory activity in both nude mice and human cell lines (Fairied et al. 2007; Kaur et al. 2009). Inflammatory disorders are mainly characterized by the production of significant amounts of nitrogen reactive species (NOS), free radicals species (ROS) and cytokines such as IL-1β, IL-6 and TNF-α (Federico et al. 2007). The inhibition of the cytokines, recognized as pro-inflammatory, was identified as a target for anti-inflammatory therapies. Thus, the anti-inflammatory effect of 1 is due to its ability to suppress IL-6 expression (BenSaad et al. 2017).

Ellagic acid (2) is a dimeric derivative of gallic acid. It is a phenolic acid found in the Vitis amurensis berry (Zhao et al. 2011). It is known for its antioxidant activity. It inhibits in vitro lipid peroxidation in rat liver microsomes (Osawa et al. 1987). An anti-inflammatory activity against the inflammation, caused by the Acute Lung Injury, was also reported for 2 (Favarin et al. 2013).

The results of Losso et al. (2004) showed that 2 has an anti-proliferative activity and induces apoptosis in Caco-2, Hs 578 T and MCF-7 cancer cells with no toxic effects on the viability of normal human lung fibroblast cells. Furthermore, 2 is known for its potential anti-viral activity, mainly against human rhinoviruses (HRVs) (Park et al. 2014). Compound 2 exhibits both anti-hepatitis B virus (HBV) and anti-hepatitis C virus (HCV) functions (Wohlfarth and Effert 2009). A molecular docking analysis of 2 against the SARS-CoV-2 M^pro enzyme (PDB ID: 6LU7) showed that it interacts through hydrogen and hydrophobic bonds with the amino acid residues His41, Met49, Asn142, Gly143, Cys145 and Glu166 with a binding energy of −8.9 Kcal/mol (Adelusi et al. 2022) (Table 2). Compound 2 interacts with the RdRp residues Thr246, Arg249, Ser255 and Pro461 with a docking energy of −7.6 Kcal/mol (Gowrishankar et al. 2021) (Table 3).

Caffeic acid, ferulic acid and chlorogenic acid (compounds 3, 4 and 5, respectively) are hydroxycinnamic acids abundant in Vitis amurensis grape skin and berry (Zhao et al. 2011; Ji et al. 2015). Compound 3 is also found in coffee (Coffea arabica) and tea (Camellia sinensis L.) (Das and Eun 2016). It was shown that 3 inhibits several viruses such as HBV (Wang et al. 2009) and HPIV3 (Özçelik et al. 2011). Also, cell experiments proved that 3 influences the catalytic activity of HCoV-NL63 by blocking the virus attachment and

| Compound | Binding energy (Kcal/mol) | RdRp residues interacting with polyphenol compounds through hydrogen bonding and other interactions | Reference |
|----------|--------------------------|-------------------------------------------------------------------------------------------------|-----------|
| 2        | −7.6                     | Thr246, Arg249, Ser255, Pro461                                                                | Gowrishankar et al. 2021 |
| 6        | −7.2                     | Asp452, Lys545, Arg553, Ala554, Arg624, Ser682                                                  | Abd El-Aziz et al. 2020 |
| 7        | −8.0                     | Trp617, Tyr619, Asp760, Asp761, Trp800, Glu811, Cys813                                        | da Silva et al. 2020 |
| 8        | −7.9                     | Trp617, Tyr619, Cys622, Asp760, Asp761, Trp800, Glu811, Cys813                                | da Silva et al. 2020 |
| 9        | −9.2                     | Trp617, Asp623, Asp760, Lys798, Glu811                                                        | da Silva et al. 2020 |
| 10       | −7.2                     | Trp617, Asp618, Tyr619, Cys622, Asp760, Asp761, Lys798, Trp800, Glu811, Phe812               | Singh et al. 2020 |
| 11       | −5.7                     | Arg553, Arg555, Thr556, Ser682                                                                | Abd El-Aziz et al. 2020 |
| 13       | −5.7                     | Lys603, Tyr606, Asp608, Pro612, Leu805, Thr806, Tyr826                                    | Mhatre et al. 2021 |
| 14       | −9.8                     | Tyr456, Arg555, Thr556, Tyr619, Pro620, Lys621, Asp623, Arg624, Thr680, Ser682, Thr687, Ala688, Asn691, Ser759, Asp760 | Iheagwam and Rotimi 2020 |
| 16       | −8.3                     | Ser514, Arg553, Asp616, Asp623, Asp761, Ala762, Trp800                                     | Joshi et al. 2021 |
limiting, therefore, its replication (Zhang et al. 2020). Furthermore, 3 was described as a blocker of PKA1 (RAC/CDC42-activated kinase 1) (Xu et al. 2005) which is the major “pathogenic” kinase. The abnormal activation of PKA1 causes a large variety of diseases/disorders including inflammation, malaria and pandemic viral infections such as influenza and human immunodeficiency virus (HIV) (Maruta and He 2020). A docking analysis on the role of 3 as a ligand for the SARS-CoV-2 Mpro (PDB ID: 6LU7) proved its ability to interact with the target enzyme through hydrogen bonds with the residues Gly143, Ser144, Cys145 and His163 and a binding energy of −5.7 Kcal/mol (Kumar et al. 2021). For these reasons, 3 is considered as a potential inhibitor of the SARS-CoV-2 Mpro.

Compound 4 is a ubiquitous natural phenolic phytochemical. It is commonly found in various plants such as cereals, vegetables, fruits, flowers, beans, coffee and nuts (Kumar and Pruthi 2014). Compound 4 is an antioxidant (Ferreira et al. 2020). It also has an anti-inflammation effect (especially in the lungs) and it protects the lungs against the viral infections by the amplification of the Toll-like receptor 7 (TLR7) and the mitochondrial anti-viral-signaling protein (MAVS) signaling functions (McCarty and DiNicolantonio 2020). The anti-viral activity of 4 was proved against the mouse hepatitis virus (MHV) (Kim et al. 2008). Data of molecular docking showed that 4 binds to the SARS-CoV-2 Mpro protein (PDB ID: 6LU7) through hydrogen bonds with the amino acid residues Glu14, Met17, Gly71 with a binding energy of −5.4 Kcal/mol (Salman et al. 2020). Nonetheless, 4 has better interactions with the three structural proteins: E (PDB ID: 2MM4), M (PDB ID: 4FB1B) and N (PDB ID: 6M3M) (Bhowmik et al. 2020).

Compound 5 is an ester, formed between caffic acid and quinic acid. It is abundant in Vitis amurensis grape skin (Ji et al. 2015). Compound 5 has noteworthy pharmacological effects, such as antioxidant, hypoglycemic, anti-tumor, anti-coagulant and anti-viral (Hu et al. 2006; Chen et al. 2008). It was shown that 5 plays a significant role in preventing the viral infection in the early stages of the virus growth. For example, it has a strong inhibitory effect against porcine parvovirus (PPV) (Sheng et al. 2008). In vitro anti-viral experiments revealed a concentration dependent effect of 5 on HSV infection (Yarmolinsky et al. 2012). Besides, 5 is an inhibitor of the adenovirus ADV-11 (Chiang et al. 2002), the enterovirus EV71 (Li et al. 2012) and IAV (H1N1) (Liu et al. 2016). The work of Patil et al. (2021), based on in silico results, showed that 5 interacts with the active site of the SARS-CoV-2 Mpro (PDB ID: 6LU7) through hydrogen bonds with the amino acid residues His41, Phe140, Leu141, His163, Glu166 and Thr190 (Table 2). These interactions have a binding energy of −6.0 Kcal/mol. Consequently, 5 can be considered as potential candidate for SARS-CoV-2 inhibition.

6.2. Flavonoids

Flavonoids, which are an important class of polyphenols in Vitis amurensis, are present mainly in berry, grape skin, seed, root and leaf (Wang et al. 2000; Zhao et al. 2011; Ji et al. 2015; Kedrina-Okutan et al. 2019). Flavonoids are bioactive compounds and they have various health-promoting effects. They can be used as drugs to prevent ROS regeneration (Lale et al. 1996). The anti-viral activity of many flavonoids was reported against various viral strains. Flavonoids exert their anti-viral effects through the blockage of cellular receptors, inhibition of the viral antigenic determinants and the loss of enzymatic functions (Evers et al. 2005).

Quercetin (6) is considered as one of the most important flavonoids, mainly flavonols-type in Vitis amurensis root (Zhao et al. 2011). Compound 6 is ubiquitously present in various vegetables such as peas (Pisum sativum), onion (Allium cepa), in fruits such as apple (Malus pumila), mulberry (Morus alba), apricot (Prunus armeniaca) and in medicinal plants such as Jaman (Eugenia jambolana Lam.), neem (Azadirachta indica), arjan (Terminalia arjuna), peepal (Ficus religiosa) and aloevera (Aloe barbadensis) (Sultana and Anwar 2008). Compound 6 has several potential biological activities including antioxidant, anti-inflammatory, anti-allergic and anti-viral (D’Andrea 2015; Liu et al. 2016). The anti-viral activity of 6 was essentially displayed against HCV (Rojas et al. 2016), IAV (Liu et al. 2016), EV71 (Yao et al. 2018) and SARS-CoV (Nguyen et al. 2012). Also, 6 has anti-viral effects on SARS-CoV-2. Khaerunnisa et al. (2020) used molecular docking study to prove the ability of 6 to bind with the active site of the SARS-CoV-2 Mpro (PDB ID: 6LU7) at the residues His41, His164, Met165, Glu166, Asp187, Thr190 and Gln192 with a binding energy of −8.5 Kcal/mol (Table 2). These interactions have different electrostatic nature (van der Waals, π-π and π-sulfur). Compound 6 can bind to the active site of the SARS-CoV-2 RdRp (−7.2 Kcal/mol) and it is described as a candidate for RdRp inhibiting (Abd El-Aziz et al. 2020) (Table 3). It is now well established that the patients infected with SARS-CoV-2 have high levels of cytokines including TNF-α, IL-1β, IL-10 and interferon γ (Lee et al. 2020). Huang et al. (2020) indicated that the cytokine storm contributes to the disease severity and the use of the corticosteroids at the early acute infection stages may be beneficial. For this reason, the use of the anti-inflammatory agents may be considered as a promising treatment approach to relieve COVID-19 symptoms (Stebbing et al. 2020). Accordingly, 6 is a potent candidate against infections due to the COVID-19 proliferation. Indeed, 6 inhibits interleukins production and regulates the TNF and AMP activated protein kinase (MAPK) signaling pathways (Kashyap et al. 2016). In addition, 6 is recognized as a treatment of pulmonary fibrosis. It can slow down the PI3K–AKT signaling pathway by inhibiting the AKT1 expression which leads to the silence of the anti-apoptotic effect of lung fibroblast (Hohmann et al. 2019). Noteworthy, 6 decreases pulmonary arterial pressure by abolishing the proliferation of pulmonary artery smooth muscle cells and it slows down the plate-derived growth factor β signaling pathways. Thus, the cardiovascular protective effects of 6 are due to the equilibrium between ACE2-Ang1-7-Mas and ACE-AngII-AT1R (Dang et al. 2020). For all these reasons, we suggest that the use of 6 can inhibit the SARS-CoV-2 infection.

Quercetin-3-O-glucuronide (7) is a quercetin derivative that is widely distributed in Vitis amurensis berry (Zhao et al. 2011) and it forms 70.4% of the total flavonols in leaves (Kedrina-Okutan et al. 2019). Several works pointed out an anti-inflammatory activity as well as effective anti-HIV, anti-IAV and anti-HBV activities of 7 (Lee et al. 2003; Fan et al. 2011; Nosrati et al. 2018), Fan et al. (2011) indicated that 7 can suppress lung edema induced by IAV in mice. da Silva et al. (2020) showed that 7 is a promising SARS-CoV-2 inhibitor for the two enzymes Mpro and RdRp. In fact, a molecular docking analysis confirmed its interaction with SARS-CoV-2 Mpro (PDB ID: 6W63) active site through hydrogen bonds and π interactions with the amino acid residues His41, Cys145, Met165, Glu166, Arg188 and Gln189 with a binding energy of −8.5 Kcal/mol. The interaction of 7 with the SARS-CoV-2 RdRp (PDB ID: 6M71) active site, at residues Trp617, Tyr619, Asp760, Asp761, Thr810 and Cys813, has a binding energy of −8.0 Kcal/mol (da Silva et al. 2020). The interaction of 7 with the SARS-CoV-2 enzymes catalytic residues His41 and Cys145 for the Mpro as well as Asp760, Asp761 for the RdRp (Tables 2 and 3) suggests that it can play an important role in the prevention and the treatment of SARS-CoV-2.

Kaempferol-3-O-glucuronide (8) is a flavonol glycoside abundant in Vitis amurensis grape skin (Ji et al. 2015) and leaf (Kedrina-Okutan et al. 2019). It is known as an antioxidant and anti-inflammatory (Wang and Zheng 2001; Shankaran et al. 2017). Compound 8 is synthesized in the liver through the conjugation of kaempferol with glucuronate then it is transported in plasma to the body tissues (Marín et al. 2015). According to this
finding, 8 can be considered as a promising inhibitor for the SARS-CoV-2 since the virus is abundant in the plasma. Bhatia et al. (2020) detected, through a virtual screening based on molecular docking analysis, that 8 binds to the active site of SARS-CoV-2 M\textsuperscript{pro} (PDB ID: 6LU7) through one hydrogen bond with the residue His163 and several van der Waals interactions with the amino acids Thr25, Met49, Tyr54, Phe140, Asn142, Gly143, Ser144, Met165, Asp187, Arg188 and Gln189 with a binding energy of −9.8 Kcal/mol. Also, 8 was described as a potential SARS-CoV-2 RdRp inhibitor. In fact, the docking analysis of 8 on the active site of the RdRp (PDB ID: 6M71) showed that it forms hydrogen bonds, π-anion and π-alkyl interactions with a binding energy of −7.9 Kcal/mol (da Silva et al. 2020). The hydrogen bonds are formed with the amino acid residues Trp617, Tyr619, Asp761, Trp800, Glu811 and Cys813. The π-anion interactions are formed with the key enzyme residues Asp760 and Asp761. The π-alkyl interactions are formed with Cys622 and Cys813 (Table 3).

Kaempferol-3-O-rutinoside (nicotiflorin) (9), which is abundant in Vitis amurensis grape skin (Ji et al. 2015) has interesting anti-inflammatory and antioxidant activities (Gamal-Eldeen et al. 2016). Recent studies suggest that 9 can be considered as an alternative agent for decreasing cytokine levels of inflammatory markers (TNF-α, IL-1β, IL-10, IFN-γ) in COVID-19 patients.

Catechin (12) and epigallocatechin gallate (13) are polyphenolic flavan-3-ols existing in Vitis amurensis berry, grape skin and leaf (Zhao et al. 2011; Ji et al. 2015; Kedrina-Okutan et al. 2019). Compound 12 is also found in tea (Camellia sinensis L.) (Ghosh et al. 2021b). Catechins are known for their multiple health benefits such as anti-inflammatory (Yang et al. 2009), antioxidant (Singh et al. 2011), anti-tumor (Ann Bélzt et al. 2006) and anti-inflammatory (Mancini et al. 2017). Previous studies showed that catechins have potent anti-viral activities. Indeed, 12 was described as an anti-inflammatory and anti-viral activity for many viruses. In fact, negative effects of 13 were reported on several DNA viruses such as HSV-1 (Colpitts and Schang 2014), HBV (He et al. 2011) and papillomavirus (HPV) (He et al. 2013). Also, the negative effect of 13 on (+)-RNA viruses were proved on HCV (Colpitts and Schang 2014), DENV (Raekiansyah et al. 2018) and porcine reproductive and respiratory syndrome virus (PRRSV) (Zhao et al. 2014). What is more, 13 was identified as a potent against (-)-RNA viruses such as ebola virus (EBOV) (Reid et al. 2014), HIV (Li et al. 2011) and IAV (Colpitts and Schang 2014). Compound 13 blocks the early stages of viruses infection, that are attachment and genome replication (Kaihatsu et al. 2018). Nowadays, many academic researchers are focusing on the use of catechins as eventual drugs to alleviate SARS-CoV-2. In fact, the docking of 12 with the main SARS-CoV-2 protease M\textsuperscript{pro} (PDB ID: 6LU7) showed six hydrogen bonds with the amino acid residues His164, Glu166, Asp187, Thr190 and Gln192 as well as other non-covalent interactions with the residues His41, Met49 and Met165 with a binding energy of −7.9 Kcal/mol (Kaviarasu et al. 2020). Ghosh et al. (2021b) examined the effectiveness of drug candidate for COVID-19 from green tea catechins. Their docking analysis showed that 13 binds with the active site of the SARS-CoV-2 M\textsuperscript{pro} (PDB ID: 6LU7) with a binding energy of −7.6 Kcal/mol. This binding energy was due to the hydrogen bonds with the amino acid residues Thr26, His41, Leu141 and Gly143 (Sharma et al. 2022).

Myricetin (10) is a natural flavanol that occurs in Vitis amurensis berry (Zhao et al. 2011). Compound 10 reveals antioxidant properties due to its ability to scavenge ROS. For example, it inhibits the malonaldehyde (MDA) formation in rat liver microsomes (Robak and Grzylewski 1988) and it has lipoposense activity in the rat liver cytosol (Pereira and Das 1991). Additional pharmacological benefits of 10 arise from its use as antiangiogenic (Ong and Khoo 1997) and in the prevention of platelet aggregation (Tzeng et al. 1991). Compound 10 is also recognized as an antioxidant molecule in the Indian medicine (Joshi et al. 2021). Its anti-viral potential is due to its ability to inhibit the reverse transcriptase in rauscher murine leukemia virus (MULV), moloney murine leukemia virus (M−MULV) and HIV (Ono et al. 1990). Yu et al. (2012) presented 10 as SARS-CoV inhibitor since 10 interferes with the residues of the SARS-CoV helicase ATPase and it restrains its activity. It was proved that 10 can be used as a potent inhibitor against nsp15 of SARS-CoV-2. In fact, 10 showed a binding energy of −6.5 Kcal/mol when it interacts with the M\textsuperscript{pro} (PDB ID: 6LU7) amino acid residues Thr26, His41, Leu141 and Gly143 (Sharma et al. 2022).

Compound 10 exhibits a high binding affinity towards the active site of RdRp of both SARS-CoV and SARS-CoV-2 and therefore it can be anticipated to prevent the viral RNA replication (Yu et al. 2012; Singh et al. 2020). Indeed, a recent in silico study affirmed that 10 binds to the SARS-CoV-2 RdRp (PDB ID: 6M71) active site at the amino acids residues Trp617, Asp618, Tyr619, Cys622, Asp760, Asp761, Lys798, Trp800, Glu811 and Phe812 with a binding energy of −7.2 Kcal/mol (Singh et al. 2020).

Naringenin (11) is the aglycon of naringin which is recognized as the bitter component of the citrus fruits (Ameer et al. 1996). In Vitis amurensis, 11 occurs in berry (Zhao et al. 2011). It has potential biological benefits such as antioxidant and anti-inflammatory (Den Hartogh and Tsiani 2019). Compound 11 exerts inhibitory effects against HCV (Khachatourian et al. 2012), dengue virus type 2 (DENV-2) (Frabasile et al. 2017) and it stops intracellular replication of Chikungunya Virus (CHKV) (Ahmadi et al. 2016). Recent studies suggest that 11 acts as a potential inhibitor of SARS-CoV-2 (Jannat et al. 2020; Stebbing et al. 2020). The binding energy determined from the docking of 11 on the SARS-CoV-2 M\textsuperscript{pro} (PDB ID: 6LU7) active site is equal to −7.8 Kcal/mol. This binding energy is due to the hydrogen bonds with the amino acid residues His163, Cys145 and Gly143 as well as one carbon hydrogen bond and one π-alkyl interaction with respectively, the residues Gln189 and Pro168 (Jannat et al. 2020). Docking analysis results of 11 on SARS-CoV-2 RdRp (PDB ID: 6M71) revealed the existence of hydrogen bonds with the amino acid residues Arg553, Arg555, Thr556 and Ser682 with a binding energy of −5.7 Kcal/mol (Abd El-Aziz et al. 2020).

The interaction of 11 with the catalytic Cys145 is a limiting factor for the SARS-CoV-2 replication. In addition, 11 has the advantage of relieving COVID-19 symptoms (Stebbing et al. 2020). As mentioned previously, 11 has a potent anti-inflammatory activity. Therefore, it can be considered as an alternative agent for decreasing cytokine levels of inflammatory markers (TNF-α, IL-1β, IL-10, IFN-γ) in COVID-19 patients.
Procyanidins, also called condensed tannins, are polymers of flavan-3-ol units which are known for their potent antioxidant activities against 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH) (Pedan et al. 2016). The potent antioxidant activity of procyanidins, extracted from Vitis amurensis, is due to synergic effects of their ROS scavenging capacity and to their chelating effects on transition metals (Lee et al. 2009). Some studies suggested that the wild grape Vitis amurensis procyanidins exhibit an anti-inflammatory activity (Bak et al. 2013; Chen et al. 2018). In fact, the pre-treatment of human adipocytes and macrophage-like cell lines with procyanidins lead to a decrease in the IL-6 and MCP-1 and an increase in the anti-inflammatory adipokine and adiponectin production, after inflammatory stimulation (Chacón et al. 2009). In addition, a treatment of RAW 264.7 cells stimulated by lipopolysaccharide (LPS) with procyanidins, extracted from Vitis amurensis seeds, showed a decrease in the nitric oxide synthase (NOS, EC 1.14.13.39) expression and NOS production (Bak et al. 2013). The procyanidins decrease the prostaglandin E2 (PGE2) production induced by LPS. They also inhibit the expression of the pro-inflammatory mediator COX-2 (Bak et al. 2013).

Procyanidin B1 (14) is a procyanidin dimer present in Vitis amurensis berry (Zhao et al. 2011). It has an inhibitory potential on SARS-CoV (Zhuang et al. 2009). A recent molecular docking study of 14 on SARS-CoV-2 RdRp (PDB ID: 6MT1) showed a binding energy of -9.8 Kcal/mol. This binding energy was due to hydrogen bonds with the residues Tyr456, Thr556, Tyr619, Lys621, Thr680, Thr687, Asn691, Ser759 as well as to bonds with the residues Tyr456, Thr556, Tyr619, Lys621, Thr680, Thr687, Asn691, Ser759 as well as to π and van der Walls interactions with the residues Arg555, Pro620, Asp623, Arg624, Ser682, Ala688 and Asp760 (Iheagwam and Rotimi 2020). Through this study, we can assume that 14 can be implicated in the SARS-CoV-2 transmission prevention.

In Vitis amurensis, cyanidin-3-O-glucoside (15) is abundant in berry (De la Cruz et al. 2012). There are several reports that mentioned its biological effects. For example, 15 displays antioxidant and anti-inflammatory activities (Kähkönen and Heinonen 2003). It provides a protection against the endothelial dysfunction and the vascular failure as well as against the myocardial damage (Huang and Lin 1999; Ha et al. 2009). Over the last few years, stilbenes have been extensively studied because of their important biological roles such as the prevention of LDL from oxidative processes (Ngoc et al. 2008), their hepatoprotective effects (Oshima et al. 1995) and their analgesic and anti-inflammatory activities (Huang et al. 2001).

δ-viniferin (16) is a stilbene derivative that has a potent antiviral activity against a variety of viruses such as HCV (Lee et al. 2019) and HIV (Pfieger et al. 2013). Joshi et al. (2021) screened 16 against SARS-CoV-2 M\textsuperscript{pro} and RdRp enzymes. They showed that 16 binds to the SARS-CoV-2 M\textsuperscript{pro} (PDB ID: 6V2F) active site through π-π interaction with the catalytic residue His41 in addition to non-covalent interactions with the residues Thr24, Met49, Met165 and His163 with a binding energy of -8.4 Kcal/mol. Compound 16 binds to the SARS-CoV-2 RdRp (PDB ID: 7BTF) with a binding energy of -8.3 Kcal/mol through π-anion interaction with the active site catalytic residue Asp761 and non-covalent interactions with the residues Ser514, Arg553, Asp616, Asp623, Ala762, and Trp800 (Joshi et al. 2021). The intermolecular interactions of 16 with SARS-CoV-2 M\textsuperscript{pro} and RdRp proteases suggest that 16 has a high potential as a ligand against SARS-CoV-2.

6.4. Structure-Activity Relationships (SARs) of Vitis amurensis polyphenols

The strongest interaction of phenolic acids with the SARS-CoV-2 proteins resides is mainly due to the carbonyl and hydroxyl groups (Puttaswamy et al. 2020).

The high anti-viral effectiveness of the flavonols is due to the increased number of the hydroxyl groups on the B-ring. Thus, the SARS-CoV-2 M\textsuperscript{pro} inhibitory effect of myricetin, which has three hydroxyl groups (3′-OH, 4′-OH and 5′-OH) on the B-ring, is higher than that of quercetin which has two hydroxyl groups (4′-OH and 5′-OH) on the B-ring (Nguyen et al. 2021). Further, the flavonol compounds in aglycone forms have stronger antiviral activity than the glycosylated ones. Indeed, the glycosylation of quercetin at the 4′-position which leads to the formation the quercetin-3-O-gluconuride, decreases the antiviral effect of this compound. Also, the absence of the two hydroxyl groups (3′-OH and 5′-OH) on the B-ring and the glycosylation at the 4′-position of the two compounds kaempferol-3-O-glucuronide and kaempferol-3-O-rutinoside explain their lower antiviral capacity compared to myricetin, quercetin and quercetin-3-O-glucuronide (Nguyen et al. 2021).

In the flavanone group, the high inhibitory activity of naringenin against SARS-CoV-2 M\textsuperscript{pro} enzyme is due to the presence of the hydroxyl group on the 7-position at the A-ring (Nguyen et al. 2021).

In the flavan-3-ol group, the decrease in the number of hydroxyl groups leads to the decrease of the antiviral effectiveness. According to Nguyen et al. (2021), epigallocatechin gallate has higher SARS-CoV-2 M\textsuperscript{pro} inhibitory effect than catechin. Indeed, epigallocatechin gallate contains three hydroxyl groups (3′-OH, 4′-OH and 5′-OH) on the B-ring, however catechin contains two hydroxyl groups (3′-OH and 4′-OH). Also, the galloyl moiety at C3 in the C-ring molecule increases the effectiveness of the epigallocatechin gallate against SARS-CoV-2 M\textsuperscript{pro}. Zhu and Xie (2020) indicated that the dimerization of the flavan-3-ols on procyanidin B increases their inhibitory effect against SARS-CoV-2 proteins. By comparing the SARS-CoV-2 M\textsuperscript{pro} inhibitory effects of the flavan-3-ols and the flavonols, Nguyen et al. (2021) showed that the absence of the C2-C3 double bond and the C4 carbonyl on the C-ring of the flavan-3-ols lead to lower relative activity than flavonols.

In the anthocyanidins group, the SARS-CoV-2 antiviral activity of the cyaniding-3-O-glucoside is mainly due to its hydroxylation (Ghosh et al. 2021c). Also, the inhibitory activity of δ-Viniferin against the SARS-CoV-2 M\textsuperscript{pro} is due to the hydroxyl groups (Joshi et al. 2021).

7. Pharmacokinetics prediction of potential polyphenolic compounds (in silico ADMET Studies)

The prediction of the pharmacokinetics properties (ADMET) and the bioactivity of sixteen Vitis amurensis polyphenol compounds studied in the present work are screened using pkCSM (Pires et al. 2015). The molecular refractivity is predicted from SADME server (Daina et al. 2017). According to Lipinski, Ghose and Veber rules, the oral bioavailability of a drug depends on several properties. In fact, a drug must have a molecular
weight < 500 g/mol, a logP (octanol-water partition coefficient) value < 5, hydrogen bond donors (–NH or –OH groups) < 5 and hydrogen bond acceptors (N or O atoms) < 10 (Grant et al. 2006). Also, drugs should have topological polar surface area (TPSA) < 140 Å² and rotatable bonds ≤ 10 (Lipinski et al. 1997). The molar refractivity is an important property of drug-likeness and it must

| Table 4 | Prediction of the molecular and drug-likeness proprieties of polyphenols derived from Vitis amurensis. |
|---|---|
| Compound | MW | LogP | H-Do | H-Ac | Noot | TPSA | Mref | LV | GV | VV |
| 1 | 170.120 | 0.5016 | 4 | 4 | 4 | 67.135 | 39.470 | 0 | 2 | 0 |
| 2 | 302.190 | 1.1956 | 4 | 8 | 0 | 141.340 | 75.3100 | 0 | 0 | 1 |
| 3 | 180.159 | 1.1960 | 3 | 3 | 2 | 74.381 | 47.160 | 0 | 0 | 0 |
| 4 | 194.186 | 1.4896 | 2 | 3 | 3 | 66.76 | 51.630 | 0 | 0 | 0 |
| 5 | 354.311 | –0.6459 | 6 | 8 | 4 | 141.587 | 83.500 | 1 | 1 | 1 |
| 6 | 302.238 | 1.988 | 5 | 7 | 1 | 122.108 | 78.030 | 0 | 0 | 0 |
| 7 | 478.362 | –0.466 | 8 | 12 | 4 | 188.063 | 110.770 | 2 | 1 | 1 |
| 8 | 462.363 | –0.1522 | 7 | 11 | 4 | 183.269 | 108.740 | 2 | 0 | 1 |
| 9 | 594.522 | –1.3927 | 9 | 15 | 6 | 236.106 | 139.360 | 3 | 4 | 1 |
| 10 | 318.237 | 1.6936 | 6 | 8 | 1 | 126.902 | 80.060 | 1 | 0 | 1 |
| 11 | 272.256 | 2.5093 | 3 | 5 | 1 | 114.235 | 71.570 | 0 | 0 | 0 |
| 12 | 290.271 | 1.5461 | 5 | 6 | 1 | 119.662 | 74.330 | 0 | 0 | 0 |
| 13 | 458.375 | 2.2332 | 8 | 11 | 3 | 184.742 | 112.060 | 2 | 0 | 1 |
| 14 | 578.526 | 2.995 | 10 | 12 | 3 | 236.950 | 183.510 | 3 | 2 | 1 |
| 15 | 449.388 | 0.3820 | 8 | 10 | 4 | 179.740 | 108.290 | 2 | 0 | 1 |
| 16 | 454.478 | 5.6506 | 5 | 6 | 4 | 195.452 | 130.240 | 0 | 1 | 0 |

MW, molecular weight (g/mol); LogP, predicted octanol/water partition coefficient; H-Do, hydrogen bond donors; H-Ac, hydrogen bond acceptors; Noot, number of rotatable bonds; TPSA, topological polar surface area (Å²); Mref, Molar refractivity; LV, Lipinski violation; GV, Ghose violation; VV, Veber violation; Gallic acid; 2, ellagic acid; 3, caffeic acid; 4, ferulic acid; 5, chlorogenic acid; 6, quercetin; 7, quercetin-3-O-glucuronide; 8, kaempferol-3-O-glucuronide; 9, kaempferol-3-O-rutinoside; 10, myricetin; 11, naringenin; 12, catechin; 13, epigallocatechin gallate; 14, procyandin B1; 15, cyanidin-3-O-glucoside; 16, α-viniferin

| Table 5 | SwissADME pharmacokinetics prediction for polyphenols derived from Vitis amurensis. |
|---|---|
| Compound | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Absorption | 10.025 | 0.335 | 0.634 | 0.195 | –0.840 | 0.229 | –0.161 | 0.884 | 0.189 | 0.095 | 1.029 | –0.283 | –1.521 | –1.225 | 0.058 | –0.989 |
| HIA | 10.054 | 86.684 | 69.407 | 93.220 | 36.377 | 77.207 | 25.112 | 25.165 | 30.743 | 65.930 | 91.310 | 68.829 | 47.395 | 66.749 | 45.392 | 87.907 |
| Skin permeability | –2.737 | –2.735 | –2.722 | –2.722 | –2.735 | –2.735 | –2.735 | –2.735 | –2.735 | –2.742 | –2.735 | –2.735 | –2.735 | –2.735 | –2.735 | –2.735 |
| CNS permeability | –4.131 | –3.533 | –2.608 | –2.535 | –3.856 | –3.065 | –4.139 | –3.955 | –5.015 | –3.709 | –2.215 | –3.298 | –3.96 | –3.983 | –3.813 | –2.837 |
| Metabolism | 0.4466 | 0.3820 | 8 | 10 | 4 | 179.740 | 108.290 | 2 | 0 | 1 |
| Excretion | 0.537 | 0.508 | 0.619 | 0.307 | 0.407 | 0.434 | 0.503 | –0.160 | 0.422 | 0.060 | 0.183 | 0.292 | –0.085 | 0.522 | –0.101 |
| Total Clearance | 0.625 | 0.537 | 0.508 | 0.619 | 0.307 | 0.407 | 0.434 | 0.503 | –0.160 | 0.422 | 0.060 | 0.183 | 0.292 | –0.085 | 0.522 | –0.101 |
| Renal OCT2 substrate | No | No | No | No | No | No | No | No | No | No | No | No | Yes | No | No | No |
| Toxicity | 0.519 | 0.476 | 1.145 | 1.444 | –0.134 | 0.409 | 0.427 | 0.460 | 0.481 | 0.510 | –0.176 | 0.438 | 0.441 | 0.438 | 0.562 | 0.408 |
| Gallic acid | No | No | No | No | No | No | No | No | No | No | No | No | Yes | No | No | No |
| Vitis amurensis. | 2.013 | | | | | | | | | | | | | | | |
| Watersolubility (log mol/L); Caco2 permeability (log Papp in 10^-6 cm/s); HIA, Human intestinal absorption (% Absorbed); Skin permeability (log Kp); P-gp substrate, P-glycoprotein substrate; P-gpl inhibitor, P-glycoprotein I inhibitor; P-gll inhibitor, P-glycoprotein II inhibitor; VDs, volume of distribution in human body (log L/Kg); BBI permeability (log BB); CNS permeability (log PS); Total Clearance (log ml/min/Kg); Max. Tolerated dose (human) (log mg/Kg/day); LD50, Oral Rat Acute Toxicity (mol/Kg); LOAEL, Oral Rat Chronic Toxicity (log mg/Kg bw/day); Minnow toxicity (log mL); 1, gallic acid; 2, ellagic acid; 3, caffeic acid; 4, ferulic acid; 5, chlorogenic acid; 6, quercetin; 7, quercetin-3-O-glucuronide; 8, kaempferol-3-O-glucuronide; 9, kaempferol-3-O-rutinoside; 10, myricetin; 11, naringenin; 12, catechin; 13, epigallocatechin gallate; 14, procyandin B1; 15, cyanidin-3-O-glucoside; 16, α-viniferin

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range between 40 cm² and 130 cm² for an acceptable oral bioavailability (Veber et al. 2002). Out of the 16 studied compounds, only 5 Vitis amurensis polyphenols which are 3, 4, 6, 11 and 12 agree with Lipinski, Veber and Ghose rules (Table 4) and, therefore, they represent potential orally administered drugs.

Furthermore, an effective drug must have good ADMET (absorption, distribution, metabolism, excretion and toxicity) properties at a therapeutic dose (Lipinski et al. 1997). Regarding the absorption parameters, the polyphenol compounds (3, 4, 6, 11 and 12) have an optimal Caco-2 cell permeability and a good human intestinal absorption (Table 5). Compounds 4, 6, 11 and 12 are predicted to be P-glycoprotein substrates. Such drugs should be administered with a P-glycoprotein inhibitor to make easy their absorption into the cells (Lee et al. 2019). The drugs distribution results prove that 3 and 4 have the highest blood distribution (VDss). However, the flavonoids 6, 11 and 12 show the lowest distribution. Compounds 3, 4 and 11 are able to penetrate to the central nervous system (CNS) while they are poorly distributed to the blood-brain barrier (BBB). The polyphenol compounds (3, 4, 6, 11 and 12) show good metabolism since they do not express toxicity for any isoform of the cytochrome P450. These polyphenols present an excellent renal elimination and they are not renal organic transporter 2 (OCT2) substrates. Finally, these compounds do not present any toxicity effects such as mutagenicity (AMES), maximum tolerated dose, hERGI and hERGII inhibitors, oral rate acute toxicity (LD50), hepatotoxicity, skin sensation and minnow toxicity.

To conclude, according to the docking and ADME interpretation, the bioavailability and the ADMET results, we showed that these polyphenol compounds (3, 4, 6, 11 and 12) isolated from Vitis amurensis are promising drug candidates for the inhibition of the SARS-CoV-2.

8. Conclusion

COVID-19 is an important threat to the worldwide health and safety. Therefore, it is very urgent to limit its spread and diminish the mortality rate. To overcome this threat, it is essential to control its infection source and to cut off the transmission route. In the present work, the most promising anti-viral polyphenol compounds obtained from the Chinese medicinal Vitis amurensis are discussed. These compounds are expected to be potential drugs against SARS-CoV-2 disease. A molecular docking indicated that these compounds have a good binding activity with the SARS-CoV-2 enzymes M^{res} and RdRp. The anti-COVID-19 properties of the studied compounds are due to their structure-activity relationships, which prove the significant effects of the hydroxylation pattern, the glycosylation, the galloylation and the dimerization. The pharmacokinetic analysis showed that the compounds; caffeic acid (3), ferulic acid (4), quercetin (6), naringenin (11) and catechin (12) are effective inhibitors of SARS-CoV-2 because of their drug-likeness and low toxicity. These compounds are suggested as M^{res} inhibitors. Compounds 6 showed also strong binding to the RdRp (Fig. 5). The present work opens up future perspectives for the in vitro and in vivo testing possibilities of the five Vitis amurensis polyphenol compounds (3, 4, 6, 11 and 12) against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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