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Review

In silico evaluation of *Vitis amurensis* Rupr. Polyphenol compounds for their inhibition potency against COVID-19 main enzymes M^{pro} 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 unfortunatly no drugs are currently approved against this desease. Accordingly, it is of outmost 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 M^{pro} 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 M^{pro} 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.

Contents

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1. Introduction

The Severe Acute Respiratory Syndrome corona virus 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 ployphenol 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 pathogenis 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 (Walls 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).

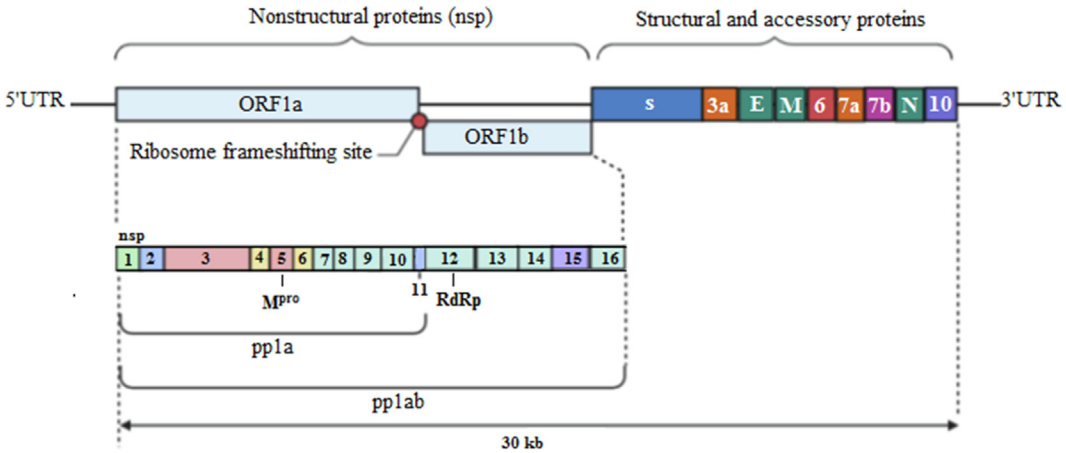

Fig. 1. Genomic organization of the Severe Acute Respiratory Syndrome SARS-CoV-2 [created with BioRender.com].

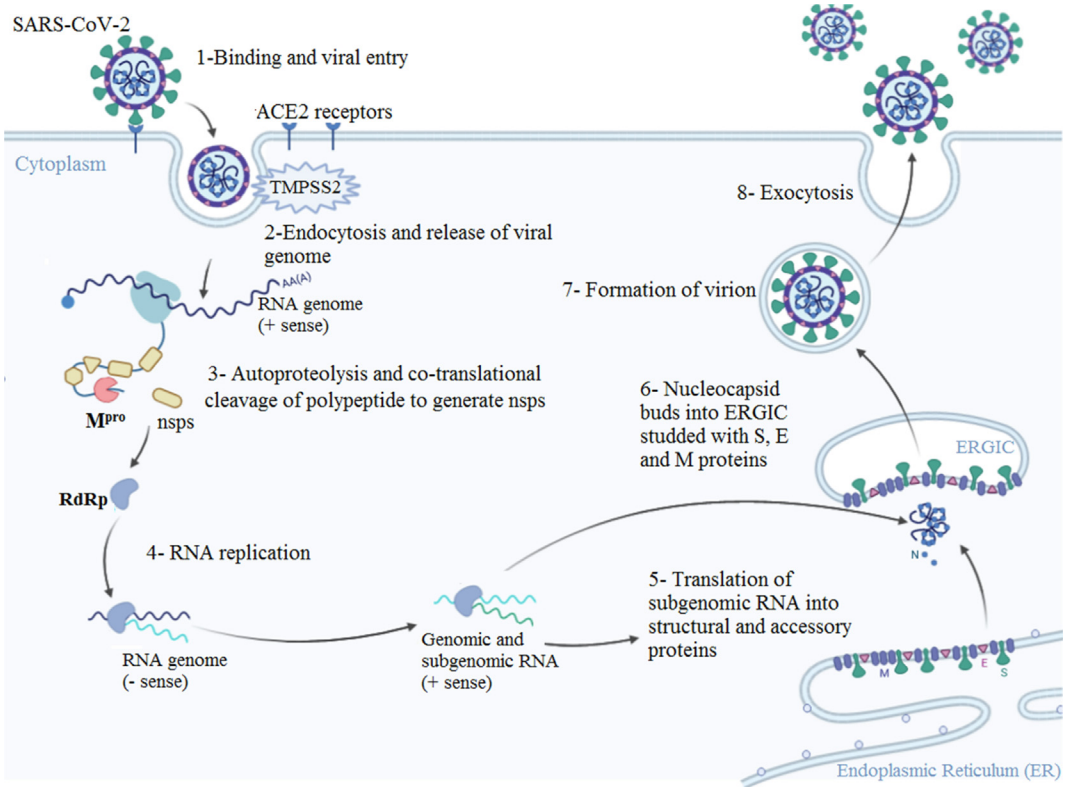

Fig. 2. Replication cycle of the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) [created with BioRender.com]. (1) The virus entry to the host cell occurs after the recognition viral spike glycoprotein-ACE2 receptor, resulting in (2) endocytosis and viral genome release in the cytoplasm. (3) Autoproteolysis induces the cleavage of the viral polyproteins by the viral protease M^{pro} to form nonstructural proteins such as RdRp for the (4) viral RNA replication. The viral RNA (+sense) undergoes translation to form the structural proteins: N, S, E and M. S, E and M are processed in the ER (5) N is processed in the cytoplasm where it brings to the replicon of the viral RNA. (6) All the viral components are combined in the ER-golgi intermediate component (ERGIC) and (7) the formed virions are released inside vesicles then (8) secreted by exocytosis outside the cell.

3. SARS-CoV-2 main enzymes

3.1. Chymotrypsin-like protease (M^{pro})

Chymotrypsin-like $3CL^{pro}$, also named M^{pro} 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 M^{pro} 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 M^{pro} (PDB ID: 6LU7) active site is composed of Thr24, Thr25, Thr26, Leu27, His41, Thr45, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, Met165, Glu166 and His172 (Fig. 3). The M^{pro} 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 M^{pro} arrests the virus multiplication inside the host cell by blocking essential processes such as viral genome replication and transcription. The sequence of the M^{pro} is highly conserved through coronavirus species. This similarity exceed 96% when compared M^{pro} from SARS-CoV-2, SARS-CoV and MERS (Ghosh et al. 2021a). This makes M^{pro} 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 M^{pro}. 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.

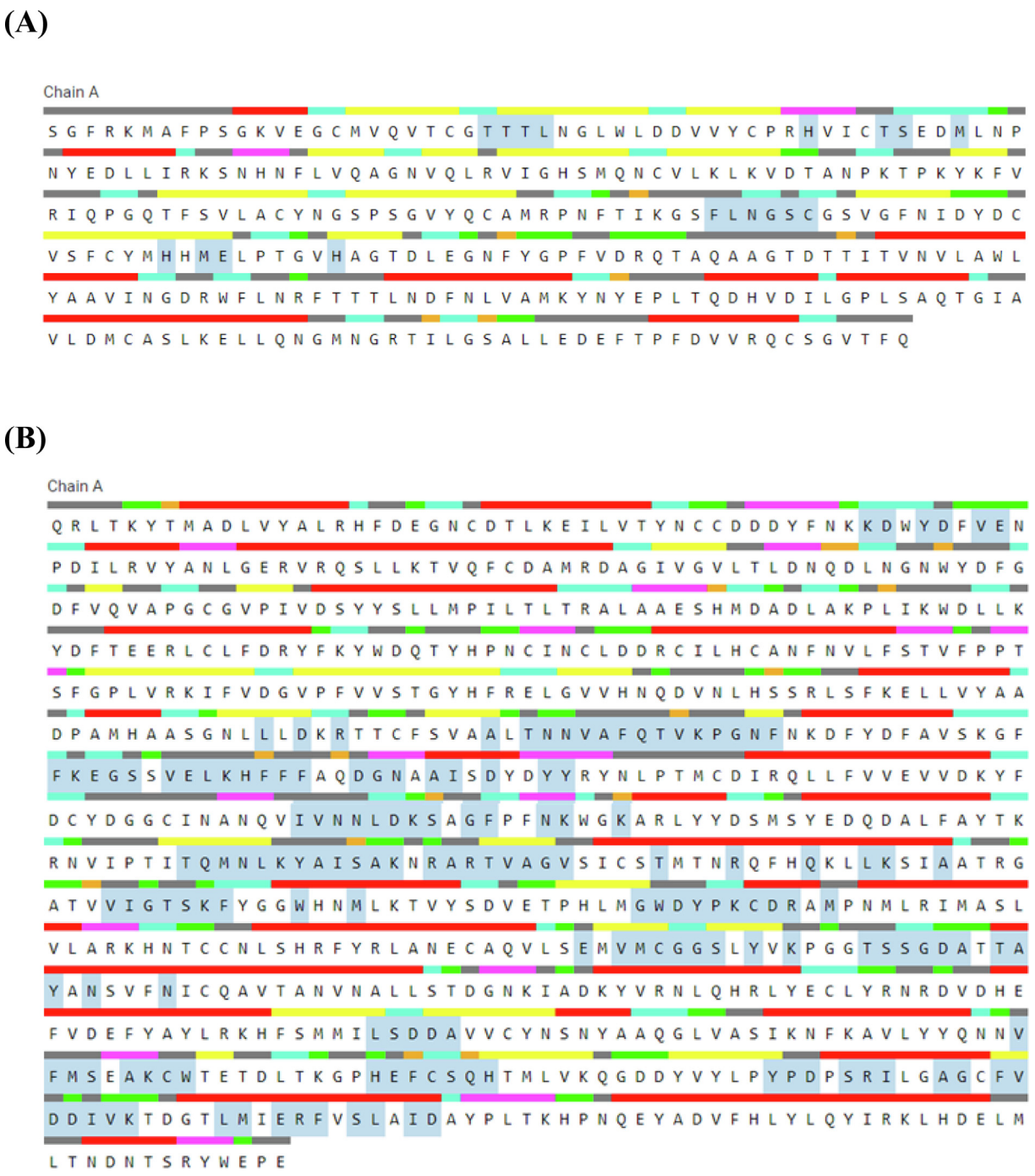

Fig. 3. Amino acid residues involved in forming the active sites for **(A)** M^{pro} (PDB ID. 6LU7) and **(B)** RdRp (PDB ID. 6NUR) [from CASTp server (www.sts.bioe.uic.edu)]. Letters highlighted in blue color show the active site residues.

4. Botanical description and therapeutic uses of *Vitis amurenis*

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 proteolitic activity of M^{pro} 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 M^{pro} and RdRp with the aid of *in silico* docking results.

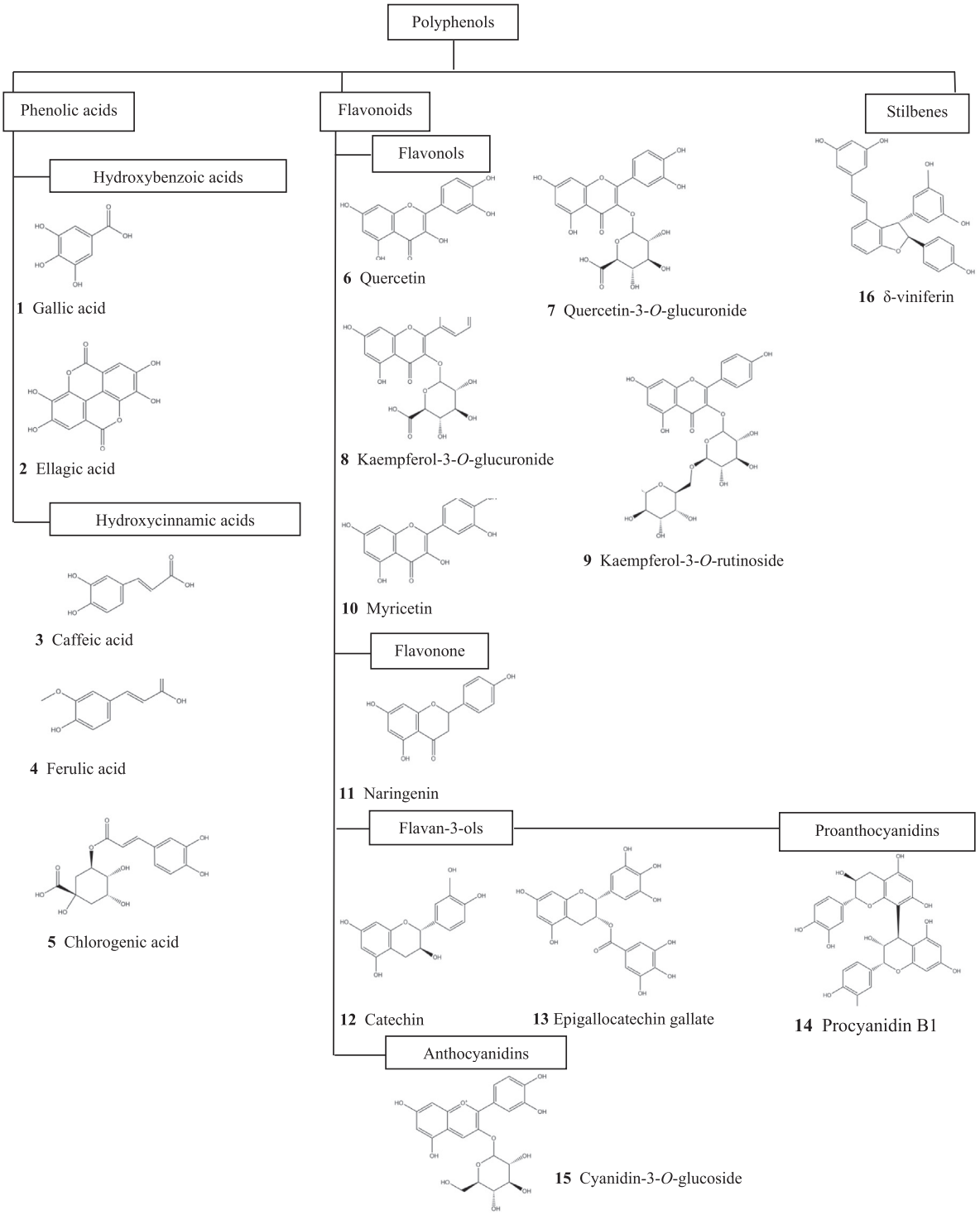

Fig. 4. Chemical structure of the studied *Vitis amurensis* polyphenols [molecules are drawn with ChemDraw 20.0]

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), flavan-3-ols (*e.g.* catechin, epicatechine 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 (C_6-C_2-C_6) 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
Antiviral effects of polyphenols derived from *Vitis amurensis*.

Compound	Part of the plant	Virus	References
1	Grape skin	HCoV-NL63 IAV HPIV3, HSV-1	Weng et al. 2019You et al. 2018Özçelik et al. 2011
2	Berry	HRVs HBV, HCV	Park et al. 2014Wohlfarth and Efferth 2009
3	Berry	HCoV-NL63 HBV HPIV3 Influenza, HIV	Zhang et al. 2020Wang et al. 2009Özçelik et al. 2011Maruta and He, 2020
4	Grape skin	MHV	Kim et al. 2008
5	Grape skin	HSV ADV-11 EV71 IAV PPV	Chiang et al., 2002; Yarmolinsky et al., 2012 Li al. 2012 Liu et al. 2016Sheng et al. 2008
6	Root	SARS-CoV IAV HCV EV71	Nguyen et al. 2012Liu et al. 2016Rojas et al. 2016Yao et al. 2018
7	Berry, leaf	HIV IAV HBV	Lee et al. 2003Fan et al. 2011Nosrati et al. 2018
9	Grape skin	IAV(H1N1 and H9N1)	Jeong et al. 2009
10	Berry	SARS-CoV HIV, MULV, M−MULV	Yu et al. 2012Ono et al. 1990Ono et al. 1990
11	Berry	HCV DENV-2 CHIKV	Khachatoorian et al. 2012Frabasile et al. 2017Ahmadi et al. 2016
12	Berry, Grape skin	IAV	You et al. 2018
13	Leaf	HSV-1 HBV HPV HCV DENV PRRSV EBOV HIV IAV	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
14	Berry	SARS-CoV	Zhuang et al. 2009
16	leaf, stem and root	HCV HIV	Lee et al. 2019Pflieger et al. 2013

Table 2
Summary of potential *Vitis amurensis* polyphenol compounds against SARS-CoV-2 M^{pro}.

Compound	Binding energy (Kcal/mol)	M^{pro} residues interacting with polyphenol compounds through hydrogen bonding and other interactions	References
1	−4.5	Leu141, Gly143, SER144, His163,Glu166	Arokiyaraj et al. 2020
2	−8.9	**His41**, Met49, Asn142, Gly143, **Cys145**, Glu166	Adelusi et al. 2022
3	−5.7	Gly143, Ser144, **Cys145**, His163	Kumar et al. 2021
4	−5.4	Glu14, Met17, Gly71	Salman et al. 2020
5	−6.0	**His41**, Phe140, Leu141, His163, Glu166, Thr190	Patil et al. 2021
6	−8.5	**His41**, His164, Met165, Glu166, Asp187, Thr190, Gln192	Khaerunnisa et al. 2020
7	−8.5	**His41**, **Cys145**, Met165, Glu166, Arg188, Gln189	da Silva et al. 2020
8	−9.8	Thr25, Met49, Tyr54, Phe140, Asn142, Gly143, Ser144, His163, Met165, Asp187, Arg188, Gln189	Bhatia et al. 2020
9	−8.9	**His41**, Met49, **Cys145**, Met165, Glu166, Thr190	da silva et al. 2020
10	−6.5	Thr26, **His41**, Leu141, Gly143	Sharma et al. 2022
11	−7.8	His163, **Cys145**, Gly143, Gln189, Pro168	Jannat et al. 2020
12	−7.9	**His41**, Met49, His164, Met165, Glu166, Asp187, Thr190, Gln192	Kaviarasu et al. 2020
13	−7.6	Thr24, Thr25, Thr26, Leu27, **His41**, Thr45, Ser46, Met49, Leu141, Asn142, Gly143, Ser144, **Cys145**, Glu166, Gln189, Gln192	Ghosh et al. 2021b
15	−8.4	Thr26, Met49, Leu141, Gly143, **Cys145**, Glu166, Asp187, Gln189	Islam et al. 2021
16	−8.4	Thr24, **His41**, Met49, His163, Met165	Joshi et al. 2021

*M^{pro} catalytic dayd (His41 and Cys145) residues are highlighted with bold font.
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; **15**, cyanidin-3-*O*-glucoside; **16**, δ-viniferin.

A virtual molecular docking study investigating commercial drugs inhibition of SARS-CoV-2 M^{pro} (PDB ID: 6LU7) showed that compound **1** induces hydrogen binding 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 (Faried 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 Efferth 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, Cys145and 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

Table 3
Summary of potential *Vitis amurensis* polyphenol compounds against SARS-CoV-2 RdRp.

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

*RdRp catalytic residues (Ser759, Asp760 and Asp761) are highlighted with bold font.
2, ellagic acid; **6**, quercetin; 7, quercetin-3-*O*-glucuronide: **8**, kaempferol-3-*O*-glucuronide; **9**, kaempferol-3-*O*-rutinoside; **10**, myricetin; **11**, naringenin; **13**, epigallocatechin gallate; **14**, procyanidin B1; **16**, δ-viniferin

limiting, therefore, its replication (Zhang et al. 2020). Furthermore, **3** was described as a blocker of PAK1 (RAC/CDC42-activated kinase 1) (Xu et al. 2005) which is the major "pathogenic" kinase. The abnormal activation of PAK1 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 M^{pro} (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 M^{pro}.

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 M^{pro} 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: 4f91B) and N (PDB ID: 6M3M) (Bhowmik et al. 2020).

Compound **5** is an ester, formed between caffeic 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 M^{pro} (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 M^{pro} (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 Walls, 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 inflammations 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 M^{pro} and RdRp. In fact, a molecular docking analysis confirmed its interaction with SARS-CoV-2 M^{pro} (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, Trp800, Glu811 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 M^{pro} 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^{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. 2004). Also, it was shown that **9** has an anti-IAV (H1N1 and H9N1) activity (Jeong et al. 2009) and it displays an active potential against M^{pro} and RdRp enzymes of the SARS-CoV-2. The docking results of da silva et al. (2020) showed that **9** presents π-π, π-sigma and π-sulfur interactions with the SARS-CoV-2 M^{pro} (PDB ID: 6W63) catalytic dyad His41 and Cys145. Furthermore, **9** shows an affinity to the SARS-CoV-2 RdRp (PDB ID: 6M71) catalytic residue Asp760 through hydrogen bond and π-anion interaction (da silva et al. 2020).

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 Gryglewski 1988) and it has lipogenase activity in the rat liver cytosol (Pereira and Das 1991). Additional pharmacological benefits of **10** arise from its use as anticarcinogenic (Ong and Khoo 1997) and in the prevention of platelet aggregation (Tzeng et al. 1991). Compound **10** is also recognized as an antitussive 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^{pro} (PDB ID: 6LU7) amino acid residues Thr26, His41, Leu 141 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 (Khachatoorian et al. 2012), dengue virus type 2 (DENV-2) (Frabasile et al. 2017) and it stops intracellular replication of Chikungunya Virus (CHIKV) (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^{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) reveled 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, IFNγ) 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 Beltz et al. 2006) and anti-allergic (Mancini et al. 2017). Previous studies showed that catechins have potent anti-viral activities. Indeed, **12** was described as an anti-pandemic IAV (H1N1) (You et al. 2018). Compound **13** has a strong 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^{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^{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, Ser144, Cys145, Glu166, Gln189 and Gly143 and to polar interactions with the residues Thr24, Thr25, Thr45, Ser46, Asn142 and Gln192. Hydrophobic interactions of **13** with the M^{pro} amino acid residues Leu27, Met49, Leu141and Met165, were also seen (Ghosh et al. 2021b). Also, **13** binds to SARS-CoV-2 RdRp (PDB ID: 6M71) with a binding energy of −5.7 Kcal/mol. This binding energy was due to hydrogen bonds with the amino acid residues Lys603, Tyr606, Asp608, Pro612, Leu805, Thr806 and Tyr826 as well as hydrophobic interactions with the residues Pro612 and Lys603 (Mhatre et al. 2021) (Table 3).

From the above discussion on the interaction of **12** and **13** with the SARS-CoV-2 M^{pro} key residues His41 and/or Cys145 one can conclude that the two flavan-3-ol derivatives may inhibit the proteolitic activity of SARS-CoV-2 M^{pro} and they may be effective towards the COVID-19 disease treatment.

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: 6M71) 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 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 (Serraino et al. 2003). A molecular docking analysis carried out by Islam et al. (2021) showed that **15** has a high binding energy (-8.4 Kcal/mol) to the SARS-CoV-2 M^{pro} (PDB ID: 6LU7) and it forms hydrogen bonds with the residues Thr26, Leu141, Gly143, Glu166, Asp187 and Gln189. In addition, **15** shows non-covalent hydrophobic interactions with the residues Met49 and Cys145. The interaction of **15** with Cys145 is the most important for SARS-CoV-2 M^{pro} inhibition.

6.3. Stilbenes

Stilbenes are polyphenolic compounds that are widely distributed in *Vitis* sp. (Dubrovina and kiselev 2017; Souid et al. 2019). In *Vitis amurensis,* stilbenes occur in leaf, stem and root (Huang and Lin 1999; Ha et al. 2009). Over the last few years, stilbenes were 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 (Pflieger et al. 2013). Joshi et al. (2021) screened **16** against SARS-CoV-2 M^{pro} and RdRp enzymes. They showed that **16** binds to the SARS-CoV-2 M^{pro} (PDB ID: 6Y2F) 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^{pro} and RdRp proteases suggest that **16** has a high potential as a ligand against SARS-CoV-2.

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

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

The high antiviral effectiveness of the flavonols is due to the increased number of the hydroxyl groups on the B-ring. Thus, the SARS-CoV-2 M^{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 lead to the formation the quercetin-3-*O*-glucuronide, 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^{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 lead to the decease of the antiviral effectiveness. According to Nguyen et al. (2021), epigallocatechin gallate has higher SARS-CoV-2 M^{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^{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^{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^{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 *SWISSADME* 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 A^2 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	Nrot	TPSA	Mref	LV	GV	VV
1	170.120	0.5016	4	4	1	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	1.4986	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	−0.4466	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	2.5099	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; Nrot, number of rotatable bonds; TPSA, topological polar surface area (A^2); Mref, Molar refractivity , LV, Lipinski violation; GV, Ghose violation; VV, Veber violation, **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**, procyanidin B1; **15**, cyanidin-3-*O*-glucoside; **16**, δ-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																
WS	−1.914	−3.181	−2.330	−2.909	−2.449	−2.925	−2.897	−2.866	−2.900	−2.915	−3.224	−3.117	−2.894	−2.892	−2.929	−2.962
Caco2 permeability	−0.026	0.335	0.634	0.195	−0.840	−0.229	−1.061	−0.884	0.189	0.095	1.029	−0.283	−1.521	−1.225	0.058	−0.989
HIA	40.154	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	−2.735	−2.742	−2.735	−2.735	−2.735	−2.735	−2.735
P-gp substrate	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P-gpI inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes
P-gpII inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Distribution																
VDss	−0.270	0.375	−1.098	−1.098	0.581	1.559	1.647	1.295	1.710	1.317	−0.015	1.027	0.806	−0.158	1.464	−2.013
BBB permeability	−1.424	−1.272	−0.647	−0.280	−1.407	−1.098	−1.614	−1.441	−1.669	−1.493	−0.578	−1.054	−2.184	−1.940	−1.713	−1.188
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																
CYP2D6 substrate)	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
CYP1A2 inhibitor	No	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
CYP2C9 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No
Excretion																
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	No	Yes	No	No
Toxicity																
AMES toxicity	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Max. Tolerated dose	0.519	0.476	1.145	1.444	−0.134	0.499	0.427	0.460	0.481	0.510	−0.176	0.438	0.441	0.438	0.562	0.408
hERGI inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
hERGII inhibitor	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes
LD50	2.03	2.399	2.383	2.322	1.973	2.471	2.497	2.513	2.513	2.497	1.791	2.428	2.522	2.482	2.549	2.606
LOAEL	3.241	2.698	2.092	1.794	2.982	2.612	4.510	4.641	3.569	2.718	1.944	2.5	3.065	4.349	4.201	3.309
Hepatotoxicity	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Skin sensitization	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Minnow toxicity	1.938	2.110	2.246	2.074	5.741	3.721	8.323	6.898	6.252	5.023	2.136	3.585	7.713	8.704	6.398	0.503

WS, Water solubility (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-gpI inhibitor, P-glycoprotein I inhibitor, P-gpII inhibitor, P-glycoprotein II inhibitor, VDss, volume of distribution in human body (log L/Kg); BBB 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 mM); **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**, procyanidin B1; **15**, cyanidin-3-*O*-glucoside; **16**, δ-viniferin

range between 40 cm^3 and 130 cm^3 for an acceptable oral biovailability (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) but 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), heptatotoxicity, skin sensation and minnow toxicity.

To conclude, according to the docking analysis interpretation, the bioavailability and the ADMET results, we showed that these polyphenol compounds (**3**, **4**, **6**, **11** and **12**) isolated from *Vitis amurenis* 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^{pro} and RdRp. The anti-COVID-19 properties of the studied compounds are due to their structure-activity relationships that 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^{pro} 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.

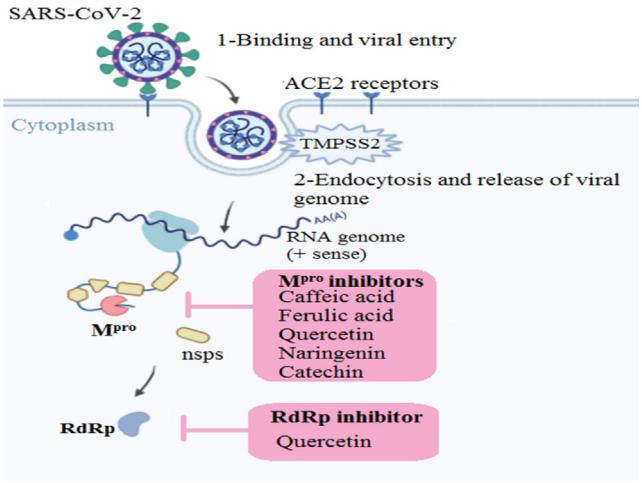

Fig. 5. Schematic representation of the SARS-CoV-2 protease inhibitory effects of some *Vitis amurensis* polyphenols selected according to their drug-likeness characteristics [created with BioRender.com]

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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