REVIEW

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In silico approach of secondary metabolites from Brazilian herbal medicines to search for potential drugs against SARS-CoV-2

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The new severe acute respiratory syndrome coronavirus (SARS-CoV-2) recently emerged as a worrying pandemic, with many confirmed cases and deaths globally. Therefore, there is a clear need for identifying effective therapeutic options and a review of secondary metabolites related to Brazilian herbal medicines was performed as a strategy for the discovery of new antiviral agents. To confirm this potential, an in silico screening of the identified compounds identified was also evaluated. The review was performed by the PubMed database and the selected natural compounds were subjected to in silico analysis such as QSAR, molecular docking and ADMET. 497 secondary metabolites were identified from 23 species. The in silico assays indicated 19 potential anti-SARS-CoV-2 compounds, being triterpenes and phenolic compounds. The indicated compounds showed a high affinity with proteins considered as the main molecular targets against SARS-CoV-2 and parameters indicated low toxicity. In addition to Brazilian medicinal plants, these compounds can be found in other species and they can be a base for the synthesis of other anti-COVID-19 drugs. Therefore, this review is important to conduct researches that address the emerging need for drugs in COVID-19 treatment.

KEYWORDS
Brazilian botanical species, COVID-19, phenolic compounds, secondary metabolites, triterpenes

1 | INTRODUCTION

After SARS-CoV-2 initial discovery, the World Health Organization declared a pandemic situation, with over 30.6 million confirmed cases globally and more than 954,000 deaths as of September 2020 (Worldometer, 2020). Although clinical trials have been conducted with several drugs as remdesivir, favipiravir, chloroquine, hydroxychloroquine, ribavirin, tocilizumab, and sarilumab (Lu et al., 2020), there is no scientific evidence of an effective treatment for

Coronavirus Disease 2019 (COVID-19). In addition, the discovery and production of a safe and effective vaccine can take months or even years, highlighting the need for identifying effective therapeutic options in response to the growing number of cases and deaths resulting from this pandemic.

Plants species have been of great importance for human development and Brazil is the country with the largest biodiversity in the world, presenting a rich chemical diversity of secondary metabolites, which is a potential source of new drugs (Valli & Bolzani, 2019). Although secondary metabolites are compounds non-essential for plant basic vital functions, they present several pharmacological

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properties, including antiviral activity (Troost et al., 2020; Zakaryan et al., 2017; Zhou et al., 2017).

Based on this reality, reviews guided by in silico analysis has proved valuable in the initial large-scale screening of compounds that present antiviral effect and inhibit important target proteins. Several authors have been using in silico tool to find potential COVID-19 treatment options (Arya et al., 2020; Hall & Ji, 2020; Qamar et al., 2020; Wu et al., 2020). Among the SARS-CoV-2 targets studied are the spike glycoprotein (S protein), which mediates the entry of the virus into the cell (Walls et al., 2020), as well as the papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro) that are related to viral protein processing (Harcourt et al., 2004; Yang et al., 2005). The RNA-dependent RNA polymerase (RdRp) is also a key target since it catalyzes the viral RNA synthesis and plays a central role in the replication and transcription cycle of SARS-CoV-2 (Gao et al., 2020).

In this context, this work aimed to identify secondary metabolites from licensed Brazilian native species as a source for new antiviral agents and confirm their potential to treat SARS-CoV-2 infection using an in silico approach.

2 | MATERIALS AND METODS

2.1 | Literature search and compound selection from Brazilian native species

The Brazilian native species "*Ananas comosus*", "*Anadenanthera colubrina*", "*Bacopa monieri*", "*Brosimum gaudichaudii*", "*Caesalpinia ferrea*", "*Carapichea ipecacuanha*", "*Cereus jamacaru*", "*Cereus peruvianus*", "*Cordia curassavica*", "*Croton heliotropiifolius*", "*Dorstenia aritoflia*", "*Erythrina velutina*", "*Erythrina verna*", "*Himatanthus lancifolius*", "*Lantana camara*", "*Maytenus ilicifolia*", "*Mikania glomerata*", "*Myroxylon balsamum*", "*Operculina hamiltonii*", "*Passiflora alata*", "*Paullinia cupana*", "*Schinus terebinthifolia*", "*Senna alexandrina*", "*Solanum paniculatum*", "*Stryphnodendron adstringens*", "*Trichilia catigua*", and "*Uncaria tomentosa*" (Carvalho et al., 2018) were used as query keyword on PubMed database. Studies published from January 1st 2005 to March 31st 2020 were selected. Reviews studies, studies related only to biological assays and wrote in non-English language were excluded. The secondary metabolites reported in studies on chemical characterization of extracts were tabulated and classified according to their biosynthetic pathways. Repeated references to the same compound were excluded.

2.2 | Quantitative structure–activity relationship (QSAR) analysis

Aiming to predict the antiviral potential, the compounds were subjected to quantitative structure–activity relationship (QSAR) analysis using the platform Prediction of Activity Spectra for Substances (PASS online). Their structure was compared with substances available in the database that are active against the virus. The action specifically on Rhinovirus and Picornavirus were selected due these species belong to the same Coronavirus group ([+]ssRNA - Group IV) (Fernández-Miragall et al., 2009; Kim et al., 2012; Schrauf et al., 2009; Zhu et al., 2020a). The probabilities of each compound to be active (Pa) and inactive (Pi) were reported and the compounds that showed Pa–Pi ≥0.5 results at least one of the viruses were selected for further analysis (Seibert et al., 2019).

2.3 | Molecular docking analysis

The compounds selected in the previous step were subjected to molecular docking analysis by the AutoDock Vina tool using PyRx software in order to understand the interaction between these compounds and the target proteins to combat the SARS-CoV-2 infection (Dallakyan & Olson, 2015). Crystalline structures of SARS-CoV-2 (2019-nCoV) papain-like protease (PLpro) (Protomer PDB ID 6W9C), main protease, also called 3-Chymotrypsin-like protease (3CLpro) (PDB ID 6Y2F), spike glycoprotein (S protein) (Protomer PDB ID 6VSB) and RNA-dependent RNA polymerase (RdRp) (PDB ID 6 M71) were obtained from the protein database (PDB). 3D structure of the selected compounds and controls (formoterol, disulfiram, nelfinavir, prulifloxacin, hydroxychloroquine, arbidol, remdesivir and favipiravir) (Arya et al., 2020; Chen et al., 2020; Fantini et al., 2020; Lin et al., 2018; Qamar et al., 2020; Wang et al., 2020; Zhu, Lu, et al., 2020) were obtained by the PubChem database. The files were converted to the appropriate format (*.pdb) using the Biovia Discovery Studio software (San Diego, USA). Then, an algorithm method was used to calculate the binding energies between the targets and the compounds by the PyRx docking tool.

2.4 | Drug-like prediction and ADMET profile

The compounds that showed the best results on molecular docking analysis were subjected to the web-based tool ADMETlab (Dong et al., 2018) to predict the drug-likeness based on Lipinski's rule and some ADMET (absorption, distribution, metabolism and excretion - toxicity) parameters.

3 | RESULTS AND DISCUSSION

3.1 | Literature search and compound selection

The presence of different biomes in Brazil means that the country has the greatest biodiversity in the world. Although Brazilian plants have a wide chemical variety, few products from these species have been developed (Valli & Bolzani, 2009). Difficulty in accessing medicinal plants is one of the factors that hinder research and the production of medicines. For this reason, Brazilian native species that are found on the herbal medicine market were selected in this study in order to

facilitate access to the natural product and enable the development of research for future in vitro and in vivo assays.

In this way, 497 secondary metabolites were identified from 23 species (Table S1–S4). On the other hand, no secondary metabolite has yet been identified in the extracts from *Cereus peruvianus*, *Cordia curassavica*, *Croton heliotropiifolius* and *Operculina hamiltonii*. Three main classes generally considered were: alkaloids (11%), phenolic compounds (42%), steroids and terpenes (43%). In addition, furan derivates (1%) and lactones (3%) were also reported (Figure 1).

Among the species selected in this review, *Anadenanthera colubrine* (Vigerelli et al., 2014), *Caesalpinia ferrea* (Lopes et al., 2013; Marques et al., 2015), *Lantana camara* (Hasan, 2017), *Maytenus ilicifolia* (Khon et al., 2012), *Schinus terebinthifolia* (Nocchi et al., 2017), *Solanum paniculatum* (Valadares et al., 2009), *Stryphnodendron adstringens* (Felipe et al., 2006), *Trichilia catigua* (Espada et al., 2015) and *Uncaria tomentosa* (Caon et al., 2014; Reis et al., 2008) have already demonstrated action against different viruses which supports the antiviral potential of their constituents.

3.2 | Quantitative structure–activity relationship (QSAR) analysis

The previously identified compounds were subjected to QSAR analysis in order to select the best antiviral agents. This analysis was performed using antiviral activity against Rhinovirus and Picornavirus, which belong to the same SARS-CoV-2 group ([+]ssRNA - Group IV),

since the emergence of the new coronavirus is recent and few studies have proven the efficacy of drugs against this virus.

As observed in Figure 2, coumarin, phenolic acid and derivates, monoterpene and steroid showed the best result for this analysis, since more than half of the compounds for these classes showed Pa– Pi ≥0.5 results. In this way, coumarin has already shown inhibitory action against different viruses and its mechanism of action is related to the inhibition of proteins essential for virus survival (Mishra et al., 2020). In accordance with our results, Özçelik et al. (2011) observed that phenolic acids, such as gallic acid and quinic acid, showed an antiviral effect greater than compounds belonging to alkaloid and flavonoid classes. In addition, monoterpenes and steroids can be highlighted and previous studies support this prediction for both classes (Astani et al., 2010; Gu & Hao, 2016).

The complete QSAR analysis for all compounds is shown in the supplementary material (Table S1–S4). All these data confirm the potential of secondary metabolites as antiviral agents and reinforce the importance of this study as a quick screening for the selection of the best candidates for the COVID-19 treatment.

3.3 | Molecular docking analysis

The molecular docking results of the natural compounds were analysed in comparison to control drugs (Table S5) and the results of the selected compounds are shown in Table 1. The reference drugs are among the main ones indicated for the COVID-19 treatment by
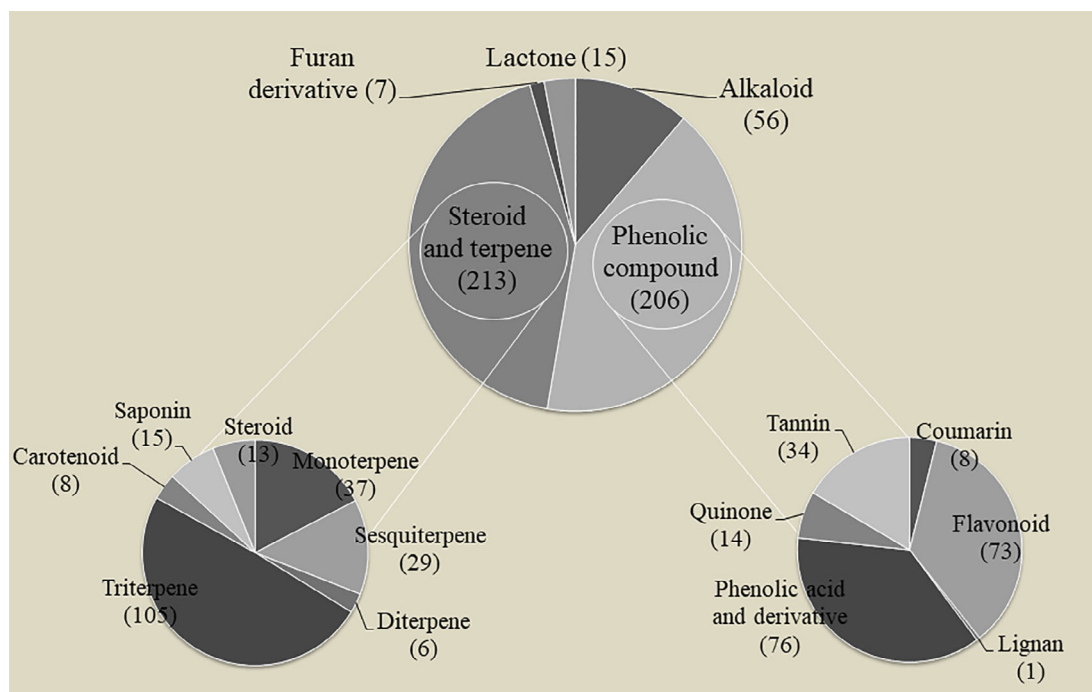

FIGURE 1 Secondary metabolites reported in studies on chemical characterization of extracts from Brazilian native species [Colour figure can be viewed at wileyonlinelibrary.com]
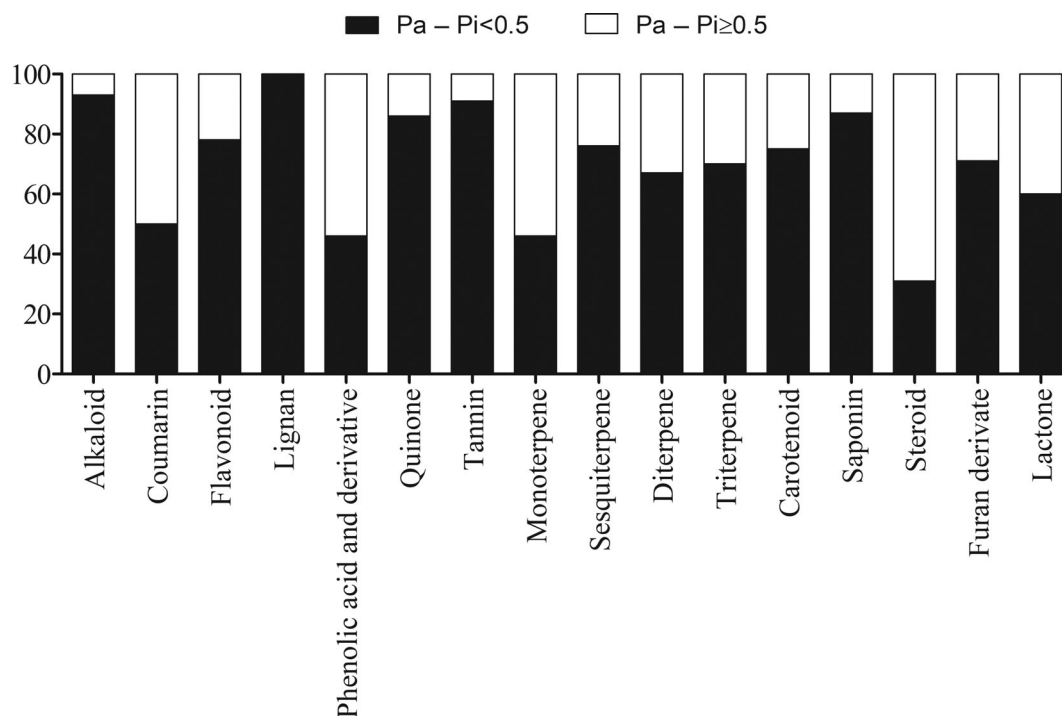
FIGURE 2 Proportional result according to the secondary metabolites class that showed Pa–Pi < 0.5 or Pa–Pi ≥ 0.5 values by quantitative structure–activity relationship (QSAR) analysis using the PASS online tool

TABLE 1 Quantitative structure–activity relationship (QSAR) and molecular docking analyzes for compounds reported in native plant species licensed in Brazil with high potential against SARS-CoV-2

Compound	QSAR (Pa–Pi Value)[a]		Molecular Docking (Binding Energy Value)			
	Antiviral (Rhinovirus)	Antiviral (Picornavirus)	PLpro	3CLpro	S Protein	RdRp
(all-E)-Violaxanthin (**1**)	0.6	–	−8.0	−8.2	−8.0	−8.0
12,13-Epoxyolean-3-yl acetate (**2**)	0.5	–	−8.3	−8.8	−8.3	−8.6
12,13-Epoxyolean-9(11)en-3-yl acetate (**3**)	0.5	–	−7.8	−9.3	−8.6	−8.1
3-Geranyloxyemodin (**4**)	0.7	–	−7.4	−8.8	−7.1	−8.4
3β-Hydroxy-lantadene B (**5**)	0.5	–	−7.9	−8.3	−8.0	−7.7
Absinine (**6**)	0.5	–	−7.9	−7.8	−7.1	−9.0
Apocynin E (**7**)	0.5	–	−7.4	−8.1	−8.1	−9.3
Betulinic acid (**8**)	0.5	–	−7.9	−9.1	−7.4	−8.3
Dicaffeoylquinic acid (**9**)	0.5	0.2	−8.0	−8.2	−7.8	−8.7
Lanosta-8,24-dien-3-yl acetate (**10**)	0.7	–	−7.6	−8.8	−7.7	−8.1
Lantacin (**11**)	0.5	–	−7.7	−8.0	−8.0	−9.2
Lupenyl acetate (**12**)	0.5	–	−7.5	−8.5	−8.5	−8.5
Sigmoidin C (**13**)	0.5	–	−7.9	−9.4	−7.7	−8.4
Taraxeryl acetate (**14**)	0.6	–	−8.1	−9.1	−8.8	−8.4
Ursolic acid (**15**)	0.5	–	−7.9	−7.9	−8.3	−8.8
Ursa-9(11),12-dien-3-yl acetate (**16**)	0.5	0.1	−7.5	−8.6	−8.3	−9.0
α-Amyrin (**17**)	0.5	–	−7.5	−8.2	−8.2	−8.7
α-Amyrin acetate (**18**)	0.5	–	−7.7	−8.3	−8.1	−8.5
β-Amyrin acetate (**19**)	0.5	–	−7.6	−8.4	−8.8	−8.8

[a]Values of difference Pa–Pi. (–) Not indicated or unsatisfactory. (Pa–Pi) ≥ 0.5: high potential. 3CLpro: 3-Chymotrypsin-like protease; PLpro: papain-like protease; RdRp: RNA-dependent RNA polymerase; S protein: spike glycoprotein.

drug repurposing studies (Arya et al., 2020; Chen et al., 2020; Fantini et al., 2020; Lin et al., 2018; Qamar et al., 2020; Wang et al., 2020; Zhu et al., 2020b).

Potential anti-coronavirus therapies aim to prevent the viral life cycle and include as main targets the prevention of virus replication and RNA synthesis and the inhibition of structural proteins

(Wu et al., 2020). The first stage of the SARS-CoV-2 life cycle is the entry into respiratory cells, mediated by S protein, one of the structural proteins (Fantini et al., 2020).

The S protein forms transmembrane homotrimers protruding from the viral surface and attaches to the surface of respiratory cells using the angiotensin-converting enzyme-2 (ACE-2) as an entry
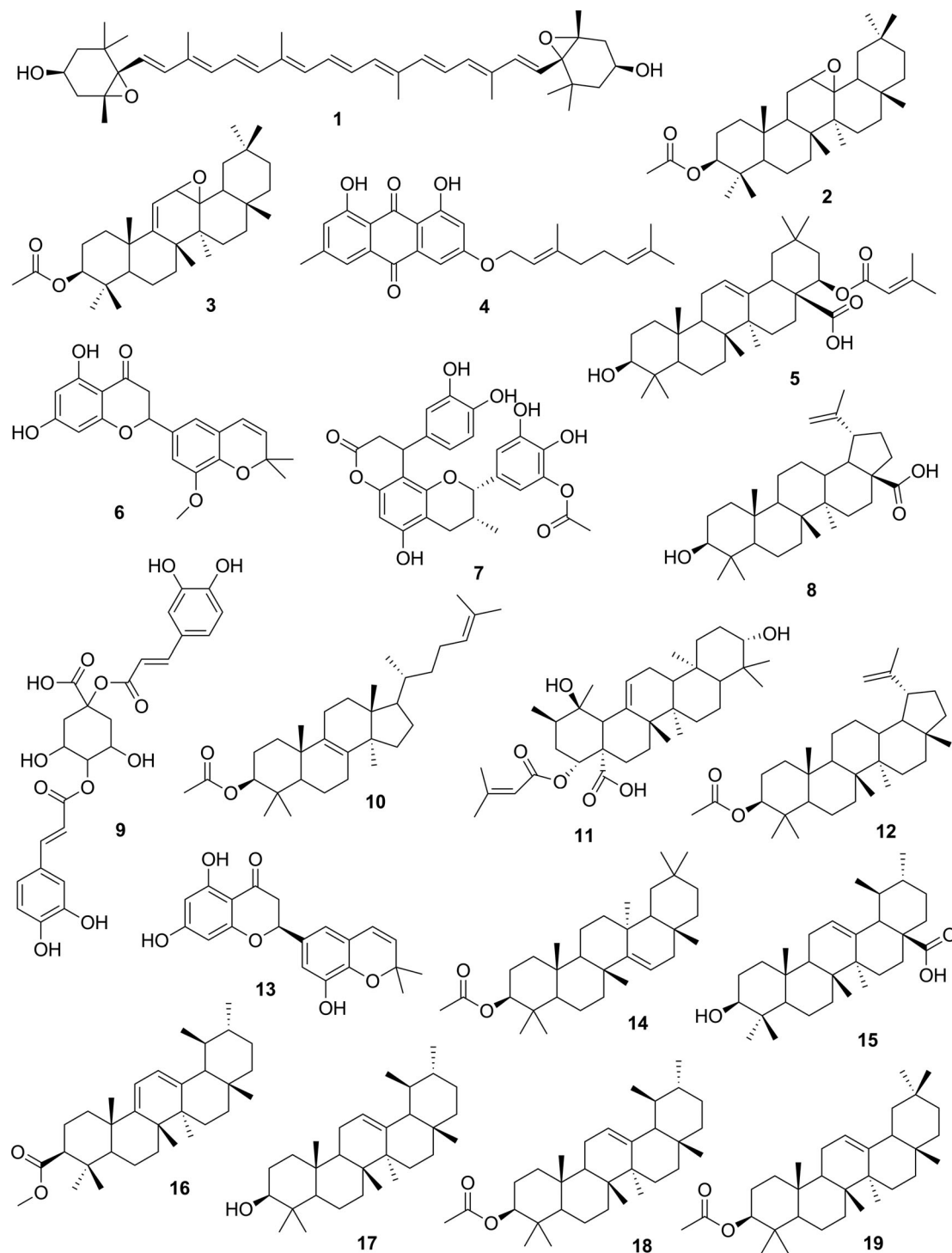

FIGURE 3   Compounds from native Brazilian species that showed the highest in silico potential anti-SARS-CoV-2. (**1**) (all-E)-violaxanthin; (**2**) 12,13-epoxyolean-3-yl acetate; (**3**) 12,13-epoxyolean-9(11)en-3-yl acetate; (**4**) 3-geranyloxyemodin; (**5**) 3β-hydroxy-lantadene B; (**6**) abssinine; (**7**) apocynin E; (**8**) betulinic acid; (**9**) dicaffeoylquinic acid; (**10**) lanosta-8,24-dien-3-yl acetate; (**11**) lantacin; (**12**) lupenyl acetate; (**13**) sigmoidin C; (**14**) taraxeryl acetate; (**15**) ursolic acid; (**16**) urs-9(11),12-dien-3-yl acetate; (**17**) α-amyrin; (**18**) α-amyrin acetate; (**19**) β-amyrin acetate

receptor (Fantini et al., 2020). The top 10 compounds for this target were **2**, **3**, **7**, **12**, **14**, **15**, **16**, **17**, **18** and **19** (Figure 3), with stronger biding energy than the hydroxychloroquine and arbidol controls. Along with arbidol, the most triterpenes bound between the subunits S1 and S2 of S protein, near to the receptor-binding domain, region that bound to the ACE-2 (Wrapp et al., 2020). Among the triterpenes, only **14**, which showed the lower binding energy (−8.8 kcal/mol), bounded in the S2 subunit, as well as the flavonoid **7** (Figure 4A and Table 1). The compound **14**, isolated from *Dorstenia arifolia*, formed hydrogen bonds with the THR1077 residue, as well as hydrophobic interactions with the Ala706, Val705, Ala713, Tyr707 and Ile712. The

binding to S2 subunit can inhibit the entry of the virus into the host cell, since this structure is responsible for the fusion of the membranes (Walls et al., 2020).

After entering the cell, the RNA released in the cytoplasm is translated into two long polyproteins, pp1a and pp1ab (Ratia et al., 2006; Ziebuhr, 2004). PLpro and 3CLpro process these polyproteins leading to the nonstructural proteins (nsp 1–16), which mediate the genome replication process (Ratia et al., 2006; Ziebuhr, 2004).

Therefore, PLpro is essential for correcting virus replication and is a possible anti-coronavirus target (Wu et al., 2020). The compounds **1**, **2**, **3**, **5**, **6**, **8**, **9**, **13**, **14** and **15** showed stronger biding energy than the
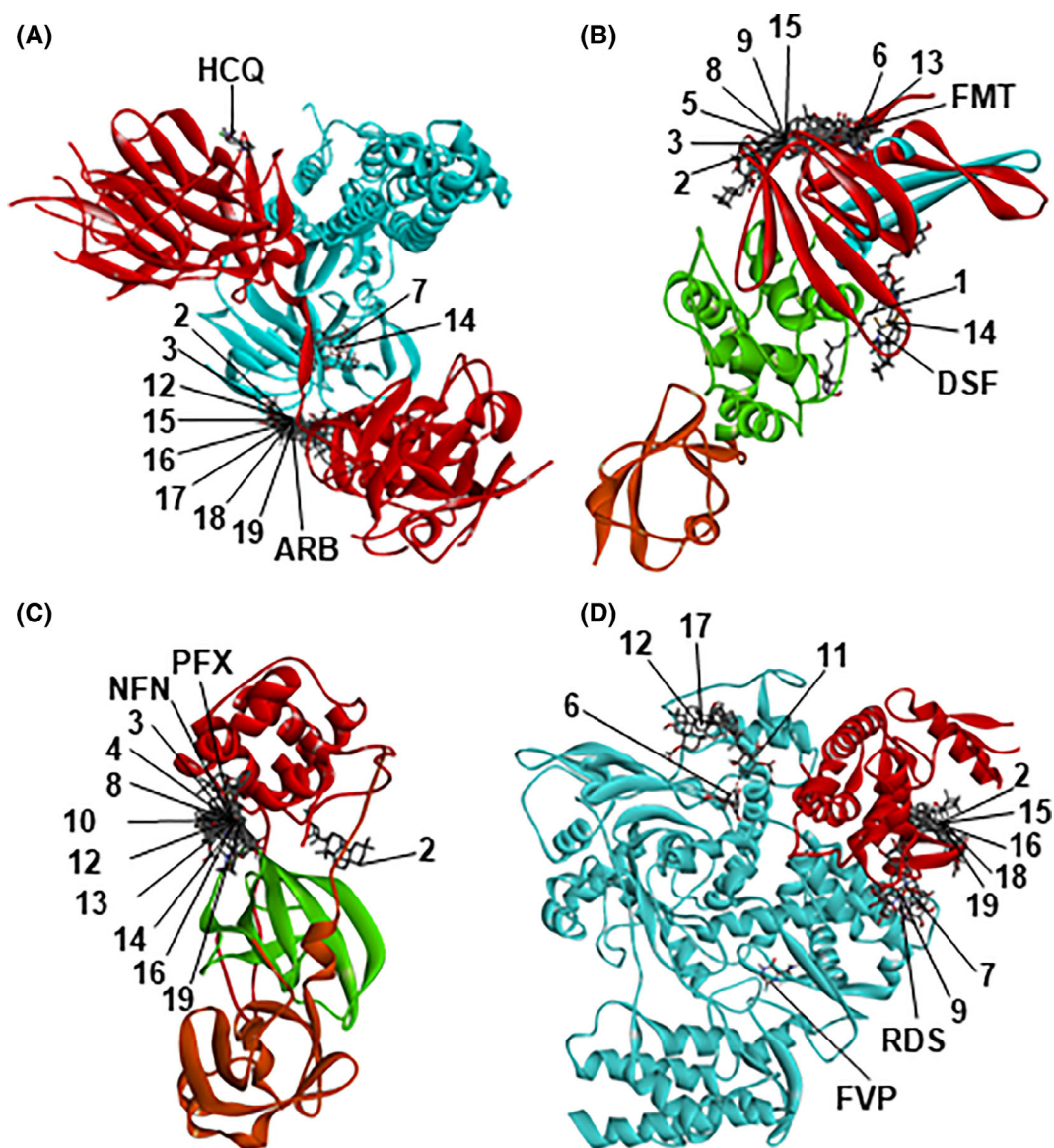

FIGURE 4 3D diagram showing the superimposed binding site of secondary metabolites and controls with (A) spike glycoprotein (S protein), (B) papain-like protease (PLpro), (C) 3-Chymotrypsin-like protease (3CLpro) and (D) RNA-dependent RNA polymerase (RdRp). (**1**) (all-E)-violaxanthin; (**2**) 12,13-epoxyolean-3-yl acetate; (**3**) 12,13-epoxyolean-9(11)en-3-yl acetate; (**4**) 3-geranyloxyemodin; (**5**) 3β-hydroxy-lantadene B; (**6**) abssinine; (**7**) apocynin E; (**8**) betulinic acid; (**9**) dicaffeoylquinic acid; (**10**) lanosta-8,24-dien-3-yl acetate; (**11**) lantacin; (**12**) lupenyl acetate; (**13**) sigmoidin C; (**14**) taraxeryl acetate; (**15**) ursolic acid; (**16**) urs-9(11),12-dien-3-yl acetate; (**17**) α-amyrin; (**18**) α-amyrin acetate; (**19**) β-amyrin acetate; (**HCQ**) hydroxychloroquine; (**ARB**) arbidol; (**FMT**) formoterol; (**DSF**) disulfiram; (**PFX**) prulifloxacin; (**NFN**) nelfinavir; (**RDS**) remdesivir and (**FVP**) favipiravir [Colour figure can be viewed at wileyonlinelibrary.com]

formoterol and disulfiram controls (Figure 4B and Table 1). Among these compounds, **2**, also isolated from *Dorstenia arifolia*, showed the best result with binding energy −8.3 kcal/mol due to hydrophobic interactions with Tyr213, Tyr305 and Lys306 residues of the PLpro fingers domain.

The compounds **1** and **14** bound near the PLpro active site, located at the bottom of the palm and thumb domains, which might interfere with substrate entering (Ratia et al., 2006). The other compounds are mainly bound between the palm and fingers domains, a region important for ubiquitin recognition (Figure 4B and Table 1). The deubiquitinating is a PLpro function involved in modulating the innate immune response (Ratia et al., 2014).

Along with PLPro, 3CLpro is another enzyme essential for cleavage of polyproteins and origin of the nsp (Ratia et al., 2006; Ziebuhr, 2004). The compounds **2**, **3**, **4**, **8**, **10**, **12**, **13**, **14**, **16** and **19** bound between II and III domains, such as nelfinavir and prulifloxacin. All the compounds showed stronger binding than

prulifloxacin (−7.6 kcal/mol). In relation to the other reference drug, only **19** did not show binding energy values lower than nelfinavir (−8.5 kcal/mol) (Figure 4C and Table 1). Comparing the values of the natural compounds, the flavanone **13**, isolated from *Erythrina velutina*, exhibited the highest binding affinity (−9.4 kcal/mol) and formed hydrogen bonds with the Asn203 and Gln110 as well as hydrophobic interactions with the Val202, Pro293 and Phe294 residues.

The inhibition of 3CLpro and PLpro by the analysed natural compounds might prevent the SARS-CoV-2 polyproteins processing (Ratia et al., 2006; Ziebuhr, 2004). The RdRp (nsp12) is one of the nonstructural proteins derived as cleavage products of these polyproteins (Gao et al., 2020). This enzyme can also be a target to drugs, since it catalyzes the RNA synthesis, being essential for replication and transcription (Chen et al., 2020; Wang et al., 2020).

The flavonoid **7**, isolated from *Trichilia catigua*, exhibited the best result for RdRp (−9.3 kcal/mol) and bound in its active site, where

TABLE 2 Data about the origin of the compounds that showed the highest in silico potential anti-SARS-CoV-2

Compound	Species	Popular Names	Local	Part	References
(all-E)-Violaxanthin (**1**)	*Ananas comosus*	Abacaxi (pineapple)	Ghana	Fruits	Steingass et al. (2020)
12,13-Epoxyolean-3-yl acetate (**2**) 12,13-Epoxyolean-9(11)en-3-yl acetate (**3**) Lanosta-8,24-dien-3-yl acetate (**10**) Lupenyl acetate (**12**) Taraxeryl acetate (**14**) Ursa-9(11),12-dien-3-yl acetate (**16**) α-Amyrin (**17**) α-Amyrin acetate (**18**)	*Dorstenia arifolia*	Caiapiá; Carapiá; Caiapiá do sul; Caiapiá preto; Capa homem; Sabuco; Sabugo do mato	Brazil	Leaves and rhizomes	Fingolo et al. (2013)
3-Geranyloxyemodin (**4**)	*Senna alexandrina*	Sene	Italy	Leaves and fruit	Epifano et al. (2015)
3β-Hydroxy-lantadene B (**5**) Betulinic acid (**8**) Lantacin (**11**)	*Lantana camara*	Camará; Cambará; Camará-de-cheiro; Camará-de-espinho; Cambará-de-cheiro; Cambará-de-chumbo; Cambará-de-espinho; Cambará-miúdo; Cambará-verdadeiro; Cambará-vermelho	Indonesia (**5**), Pakistan (**8,11**)	Aerial parts	Abdjul et al. (2017) (**5**), Begum et al. (2015) (**8**), Begum, Zehra & Siddiqui (2008) (**11**)
Absinine (**6**) Lupenyl acetate (**12**) Sigmoidin C (**13**)	*Erythrina velutina*	Mulungu	Brazil	Stem bark	Rodrigues et al. (2017) (**6**), Raupp et al. (2008) (**12**), Rodrigues et al. (2017) (**13**)
Apocynin E (**7**)	*Trichilia catiguá*	Catuaba	Brazil	Ground barks	Martins et al. (2018)
Dicaffeoylquinic acid (**9**)	*Mikania glomerata*	Guaco	Brazil	Leaves	Della Pasqua et al. (2019)
Ursolic acid (**15**)	*Maytenus ilicifolia*	Espinheira-santa	Brazil	Leaves	Wonfor et al. (2017)

hydrogen bonds with Thr710, Gly774, Lys780, Asn781 and Ser784 were formed. In addition, hydrophobic interactions with Ala706 may further direct the favorite conformation of compound **7**. The phenolic acid **9**, among the top 10 compounds with higher affinity than the controls remdesivir and favipiravir, is also bound in the RdRp active site (Figure 4D and Table 1).

The compounds **6**, **11**, **12** and **17** did not bind in the active site, but they bound in other regions of the polymerase domain and might interfere with the viral RNA synthesis (Velthuis, 2014). The other compounds, **2**, **15**, **16**, **18** and **19**, bound in the nidovirus-unique N-terminal extension domain (NiRAN) (Figure 4D and Table 1). Despite this domain is not part of the RdRp catalytic site, it is essential for the virus due to functions that may include nucleic acid ligation, mRNA capping and protein-primed RNA synthesis (Lehmann et al., 2015). Compound **15** has been reported to inhibit RdRp of the hepatitis C virus (Kong et al., 2013).

Therefore, the molecular docking results indicated that the compounds **1**–**19** showed the highest potential anti-SARS-CoV-2 (Figure 3 and Table 2). Most of them (63%, 12 compounds) are pentacyclic triterpenes. The anti-coronavirus action of different triterpenes has already been reported in the literature (Chang et al., 2012; Wen et al., 2007). Among the compounds with the best potential in silico,

8, **12** and **15** have already reported selective activity against several viruses (Chiang et al., 2005; Gómez-Calderón et al., 2017; Hong et al., 2015; Karagöz et al., 2018; Kong et al., 2013; Tohmé et al., 2019; Yu et al., 2017; Zhao et al., 2014).

The other five compounds (26%) are phenolic compounds, being one anthraquinone, one phenolic acid and three flavonoids. Most of the natural compounds recently indicated as anti-COVID-19 are phenolic compounds (Qamar et al., 2020; Wu et al., 2020). Several flavonoids have exhibited significant antiviral properties against different viruses, including coronavirus (Zakaryan et al., 2017).

3.4 | Drug-like and ADMET profile

Accordingly the Lipinski's rule, a molecule should obey four criteria to be considered as a drug-like: molecular weight ≤500 Da, number of H-bond donors ≤5, number of H-bond acceptors ≤10 and log p ≤5 (Lipinski, 2004). As observed in Table 3, only two compounds (**6** and **13**) reached all criteria of Lipinski's rule. However, several compounds that did not reach all parameters to be considered drug-like because of the log p value presented a good prediction regarding intestinal absorption (**2**, **3**, **4**, **8**, **10**, **12**, **14**, **15**, **16**, **17**, **18** and **19**). One of the

TABLE 3 Drug-like prediction and ADMET profile of the selected natural compounds

| Compound | Lipinski's Rules | | | | Human Intestinal Absorption Ideal =1 | hERG Blockers Ideal = 0 | Ames Mutagenicity Ideal = 0 | Human Hepatotoxicity Ideal = 0 |
	Molecular Weight ≤ 500	H Bond Donor ≤5	H Bond Acceptor ≤10	log p ≤5				
(all-E)-Violaxanthin (**1**)	628.938	2	4	9.75	0.651	0.506	0.446	0.000
12,13-Epoxyolean-3-yl acetate (**2**)	484.765	0	3	7.951	0.763	0.462	0.206	0.156
12,13-Epoxyolean-9 (11)en-3-yl acetate (**3**)	482.749	0	3	7.871	0.793	0.484	0.174	0.312
3-Geranyloxyemodin (**4**)	406.478	2	5	5.253	0.635	0.627	0.254	0.798
3β-Hydroxy-lantadene B (**5**)	554.812	2	4	7.722	0.697	0.424	0.090	0.308
Abssinine (**6**)	368.385	2	6	3.997	0.511	0.375	0.420	0.696
Apocynin E (**7**)	508.479	5	10	3.893	0.412	0.630	0.452	0.592
Betulinic acid (**8**)	456.711	2	2	7.09	0.791	0.421	0.090	0.188
Dicaffeoylquinic acid (**9**)	516.455	7	11	1.03	0.320	0.570	0.236	0.398
Lanosta-8,24-dien-3-yl acetate (**10**)	468.766	0	2	9.05	0.848	0.458	0.040	0.326
Lantacin (**11**)	570.811	3	5	6.692	0.697	0.415	0.090	0.368
Lupenyl acetate (**12**)	468.766	0	2	8.596	0.837	0.170	0.022	0.170
Sigmoidin C (**13**)	354.358	3	6	3.694	0.539	0.384	0.450	0.660
Taraxeryl acetate (**14**)	468.766	0	2	8.74	0.841	0.486	0.020	0.184
Ursolic acid (**15**)	456.711	2	2	7.09	0.803	0.458	0.118	0.222
Ursa-9(11),12-dien-3-yl acetate (**16**)	466.75	0	2	8.373	0.841	0.474	0.020	0.146
α-Amyrin (**17**)	426.729	1	1	8.025	0.915	0.480	0.036	0.054
α-Amyrin acetate (**18**)	468.766	0	2	8.596	0.841	0.482	0.020	0.182
β-Amyrin acetate (**19**)	468.766	0	2	8.74	0.841	0.486	0.020	0.180

most important challenges facing an oral drug is its movement across the intestinal epithelial barrier that determines the rate and extent of human absorption and ultimately affects its bioavailability (Guan et al., 2018). Despite indicating good intestinal absorption, high log P values indicate low water solubility, which can lead to low oral bioavailability. The pharmacokinetics of compounds **8**, **15** and **17** have already been studied and their oral bioavailability can be improved by formulations such as nanoemulsions, nanoparticles, liposomes, polymeric micelles and cyclodextrin complexes (Abriata et al., 2017; Cavazos-Garduño et al., 2015; Da Silva Júnior et al., 2019; Kumar et al., 2018; Liu et al., 2016; Moura et al., 2020; Qiu et al., 2019; Rodrigues et al., 2013; Soica et al., 2014; Wang et al., 2019; Zhou et al., 2019).

Regarding the possible toxic effects, the predictions of cardiotoxic (inhibition of the hERG potassium channel), hepatotoxic and mutagenic effects (Ames test) were evaluated. All the compounds that presented good prediction results of intestinal absorption also presented good prediction results regarding the toxicity effects and no compound was highly likely to be mutagenic. In vivo studies have already demonstrated low toxicity of the compounds **8** and **12** (Moura et al., 2020; Wang et al., 2019). Therefore, the compounds **1–19** may be an interesting beginning for future in vitro and in vivo tests.

3.5 | Other sources of the selected compounds

Besides the Brazilian native plants cited, the selected compounds can be extracted from other species. Some examples, which can be found in different regions of the world, are shown in the supplementary material (Table S6). These natural products can be considered as potential sources of treatment for COVID-19 and are indicated for future studies in vitro and in vitro. In addition, the possibility of research with synthetic derivatives based on the structures of compounds **1–19** is highlighted.

4 | CONCLUSION

This review is important to conduct research that addresses the emerging need for drugs in COVID-19 treatment. Based on secondary metabolites from native species found in the Brazilian herbal medicine market, the studies in silico QSAR, molecular docking and ADMET indicated potential anti-SARS-CoV-2 compounds, being mainly triterpenes and phenolic compounds. The indicated compounds showed a high affinity with proteins considered as the main molecular targets against SARS-CoV-2 and indicative of low toxicity.

In addition to Brazilian medicinal plants, these compounds can be found in other species and they can be a base for the synthesis of other anti-COVID-19 drugs. Based on the need for new drugs, the metabolomics database reported for Brazilian species can be used as a source for the assessment of other therapeutic potentials.

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SUPPORTING INFORMATION

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