



A Review of In Silico Research, SARS-CoV-2, and Neurodegeneration: Focus on Papain-Like Protease

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Abstract

Since the appearance of SARS-CoV-2 and the COVID-19 pandemic, the search for new approaches to treat this disease took place in the scientific community. The in silico approach has gained importance at this moment, once the methodologies used in this kind of study allow for the identification of specific protein–ligand interactions, which may serve as a filter step for molecules that can act as specific inhibitors. In addition, it is a low-cost and high-speed technology. Molecular docking has been widely used to find potential viral protein inhibitors for structural and non-structural proteins of the SARS-CoV-2, aiming to block the infection and the virus multiplication. The papain-like protease (PLpro) participates in the proteolytic processing of SARS-CoV-2 and composes one of the main targets studied for pharmacological intervention by in silico methodologies. Based on that, we performed a systematic review about PLpro inhibitors from the perspective of in silico research, including possible therapeutic molecules in relation to this viral protein. The neurological problems triggered by COVID-19 were also briefly discussed, especially relative to the similarities of neuroinflammation present in Alzheimer's disease. In this context, we focused on two molecules, curcumin and glycyrrhizinic acid, given their PLpro inhibitory actions and neuroprotective properties and potential therapeutic effects on COVID-19.

Keywords Molecular docking · SARS-CoV-2 · Papain-like protease · Curcumin · Glycyrrhizinic acid · Alzheimer's disease

Introduction

The first case of new coronavirus infection (coronavirus 2019; COVID-19) that causes severe acute respiratory syndrome 2 (SARS-CoV-2) (Chan et al. 2020) was identified in December 2019 in the Wuhan province, China. The disease quickly spread around the world resulting in the COVID-19 pandemic that already accounted for 515 million cases and more than 6 million deaths, according to a recent update of the World Health Organization (WHO) (2022).

Similar to SARS-CoV-2, MERS-CoV, and other animal coronaviruses, SARS-CoV-2 is part of the *Coronaviridae* family and is inserted in the genus *Betacoronavirus* (Maier et al. 2015). Coronaviruses are retroviruses with one of the

largest genomes, encoding non-structural (nsp, non-structural proteins) and structural viral proteins, including those associated with the viral envelope and involved in the cell infection process, such as the spike protein (S) that is essential for the receptor binding and viral fusion (Li 2016).

The translation of the virus replicase gene is vital to its multiplication cycle. Coronaviruses encode cysteine proteases that cleave replicase polyproteins into mature non-structural proteins. They are the papain-like proteases (PLpro), encoded by nsp3, and the major serine-like protease (3CLpro), or Mpro, encoded by nsp5 (Maier et al. 2015). It is known that continuous viral RNA synthesis depends on proteolytic processing of coronavirus replicase polyproteins. Therefore, coronavirus proteases are attractive targets for the development of antiviral drugs to reduce viral replication and its pathogenicity (Harcourt et al. 2004).

The scientific community has joined forces to face challenges raised by the pandemics, including searching for effective therapies. In emergencies, in silico tools enable maximizing knowledge about diseases and pathogens faster and at a low cost. In the drug discovery context, these approaches are efficient for molecular mechanism

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identification of potential receptor agonists or antagonists, activators or enzyme inhibitors, and ion channel openers or blockers (Cava et al. 2020; Terstappen and Reggiani 2001).

In this sense, the SARS-CoV-2 structural and non-structural proteins have been widely studied as targets for pharmacological intervention through in silico methodologies (Singh et al. 2020; Cava et al. 2020; Vardhan and Sahoo 2020; Mhatre et al. 2021; Naidoo et al. 2020; Nejat and Shahir 2021). Considering the importance of proteolytic processing by replicase polyproteins in the viral cycle and the possibility of pharmacologically intervening in this process, and in other secondary functions, PLpro presents itself as a particularly interesting focus of analysis.

Although vaccines against the virus are available, the existence of treatments is still essential and in silico studies can serve as a basis for further in vitro and in vivo tests, which can help in the development of therapies. To our knowledge, overview studies about SARS-CoV-2 and PLpro inhibitors are lacking. Besides several articles exploring this topic, a few studies include the repositioning of drugs with action on PLpro and with action on the neurological effects caused by SARS-CoV-2 infection. Based on these, we performed a systematic review on PLpro inhibitors from the perspective of in silico research and on possible therapeutic molecules in relation to this viral protein. We focus on molecular docking results given its efficiency in studying the protein–ligand molecular interactions, applicability as a screening tool and as a hypothesis testing method for probable inhibition mechanisms (Cava et al. 2020; Terstappen and Reggiani 2001). We also briefly discussed the neurological problems triggered by COVID-19, which open gaps to

relate its pathology to the neurodegeneration triggered by Alzheimer’s disease (Rahman et al. 2021b). In this context, we focused on two molecules with good therapeutic potential: curcumin and glycyrrhizinic acid.

Methods

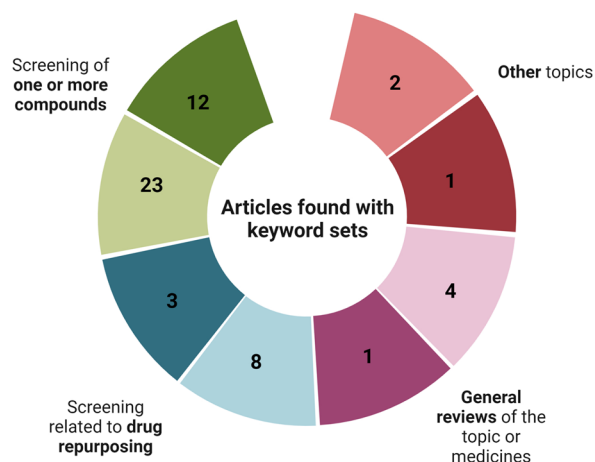
To carry out the review, we established two keyword patterns, namely: “in silico” + “COVID-19” + “papain-like protease” and “docking” + “COVID-19” + “papain-like protease.” Both were applied in the PubMed database; 17 and 37 articles referring to each set of words were found, respectively (Fig. 1). The topics included the screening of one or more compounds (12 and 23), the screening related to the repurposing of drugs (3 and 8), general reviews of the topic or of the drugs (1 and 4), and others (1 and 2). The exclusion criteria used were the existence of replicates between the lists (14) and review articles (1 for the first set and 4 for the second set of keywords). In addition, articles in other languages than English were excluded (1), as well as articles that are unavailable to the general public or those without access permission for our educational institution (3). Therefore, 31 articles were selected for reading and review. The main methods used in these works are presented in a brief way and, from the articles selected, we focus on discussion of the main findings about the phytochemicals due to their current relevance. From them, we present and discuss the main findings and methods in a succinct way, in order to gather what is essential in the literature currently referring

Fig. 1 Outline of the process of searching and selecting articles for the review

Keywords searched:

Light colors: “in silico” + “COVID-19” + “papain-like protease” (n = 17)

Dark colors: “docking” + “COVID-19” + “papain-like protease” (n = 37)



Exclusion criteria:

- Existence of **replicates** between the lists (n = 14)
- **Review** articles (1 for the first set and 4 for the second set of keywords)
- Articles in **other languages** (n = 1)
- Articles **unavailable** (n = 3)

Total: 31 articles were selected for reading and review

to PLpro and the in silico study, focusing on molecular docking.

Critical analysis of the profile of articles reveals a basic design mainly for screening studies. The dynamics that are repeated in several works include many tools of in silico research, in addition to molecular docking programs, the pharmacodynamics and pharmacokinetics programs, molecular dynamics, and the druggability of compounds, as shown in Fig. 2.

The specialized software programs used in each stage varied a lot. Although, for molecular docking, the Autodock Vina, IGEMdock, and AutoDock4 programs predominate in the protein-binding analysis. In addition, it is possible to see a predominance of local docking over blind docking. Besides, in the screening papers, there is a great concern with the protein preparation, when compared to the ligands to be tested.

Validation criteria also showed a broad spectrum, such as methods of comparison with inhibitors already described in the literature, methods of redocking, and comparison of results found between molecular docking programs. In addition, pharmacokinetic and druggability criteria proved to be particularly important in the final conclusions since the aim is the proposition of compounds and molecules that are druggable and can be used in the treatment of COVID-19 acting on PLpro. In this perspective, the great standard was the ability of the compound to remain within the criteria of Lipinsky's rule of five, which includes characteristics such as molecular weight and number of hydrogen donors that implicate in the molecule druggability (Doak et al. 2014).

Papain-Like Protease (PLpro)

PLpro is a protease that participates in the cleavage of non-structural proteins, allowing for the virus replication process. Aside from deubiquitination and deISGylating properties, PLpro plays an important role in innate immunity, since it has the ability to block the host immune system and deviate from the antiviral immune response (Mhatre et al. 2021; Osipiuk et al. 2021; Mielech et al. 2014; Shin et al. 2020; Báez-santos et al. 2020). It has also been shown that this protein can regulate IFN and NF- κ B pathways increasing antiviral signaling via TBK1 and IRF3 (Shin et al. 2020).

PLpro domains include the thumb, fingers, palm, and one with affinity for ubiquitin (Osipiuk et al. 2021; Vardhan and Sahoo 2020; Báez-santos et al. 2020). The active site of the protease is located between the subdomains of the palm and thumb and is composed of a triad, formed by the residues Cys112–His273–Asp287 (Báez-santos et al. 2020). Most of the molecules that act as inhibitors of this protein are accommodated at the S4 and S3 sites (Osipiuk et al. 2021; Báez-santos et al. 2020), while the S2 site is related

to deubiquitination and deISGylation functions (Shin et al. 2020).

Small molecules that can act as inhibitors of the main target proteins have been widely studied; new drugs, drug repurposing, derivative compounds, and natural derivatives are included (Ibrahim et al. 2020; Cavasotto and Di 2021; Srivastava et al. 2020; Thurakkal et al. 2021). In the case of PLpro, there is still a search for molecules that act on the multiple functions exerted by this protein, going beyond the inhibition of the sites involved in viral replication and including the sites responsible for deubiquitination and deISGylation (Osipiuk et al. 2021).

Since several groups of molecules have been studied, this review mainly focused on phytochemicals that have shown benefits on several conditions, which are associated with inflammation, cognitive dysfunction and others (Leitzmann 2016). Therefore, knowing the medicinal importance of these compounds, the ability of this group is believed to be useful as therapy for COVID-19. Nevertheless, the main findings regarding this protein as related to other types of compounds are available in Table 1.

In addition, in silico molecular docking studies provided useful insights to the understanding of the interaction of phytochemical class ligands with PLpro that could be used routinely before the wet screening of any phytochemicals for their antiviral, anti-inflammatory, stability, and safety aspects.

SARS-CoV-2: Focus on Papain-Like Protease Inhibitors

Phytochemicals are currently studied and are targets of in silico testing as PLpro inhibitors (Siddiqui et al. 2020; Srivastava et al. 2020; Vardhan and Sahoo 2020; Mhatre et al. 2021). Srivastava et al. (2020) applied several Withanolides, which are compounds derived from the medicinal plant *Withania somnifera* (African Flowering Plants Database, AFPD 2008), with antitumor and antiviral properties, in in silico tests on PLpro and on other SARS-CoV-2 target proteins. Among all, the withanolide B stands out, since it makes a potent allosteric bond with the protease (Srivastava et al. 2020). Furthermore, phytochemicals from *Nigella sativa* (AFPD 2008), which has terpenoids and flavonoids in their composition, were submitted on computer simulations with PLpro; however, like withanolide B, none of them interacted with the catalytic site. Nevertheless, the compounds cycloeucalenol and campesterol presented allosteric bonding with the protein accompanied by good affinity binding in a region close to the catalytic site, where the control molecules bind. The campesterol compound exhibited the best binding and had a 1000 \times higher binding energy than the controls (Siddiqui et al. 2020). In the

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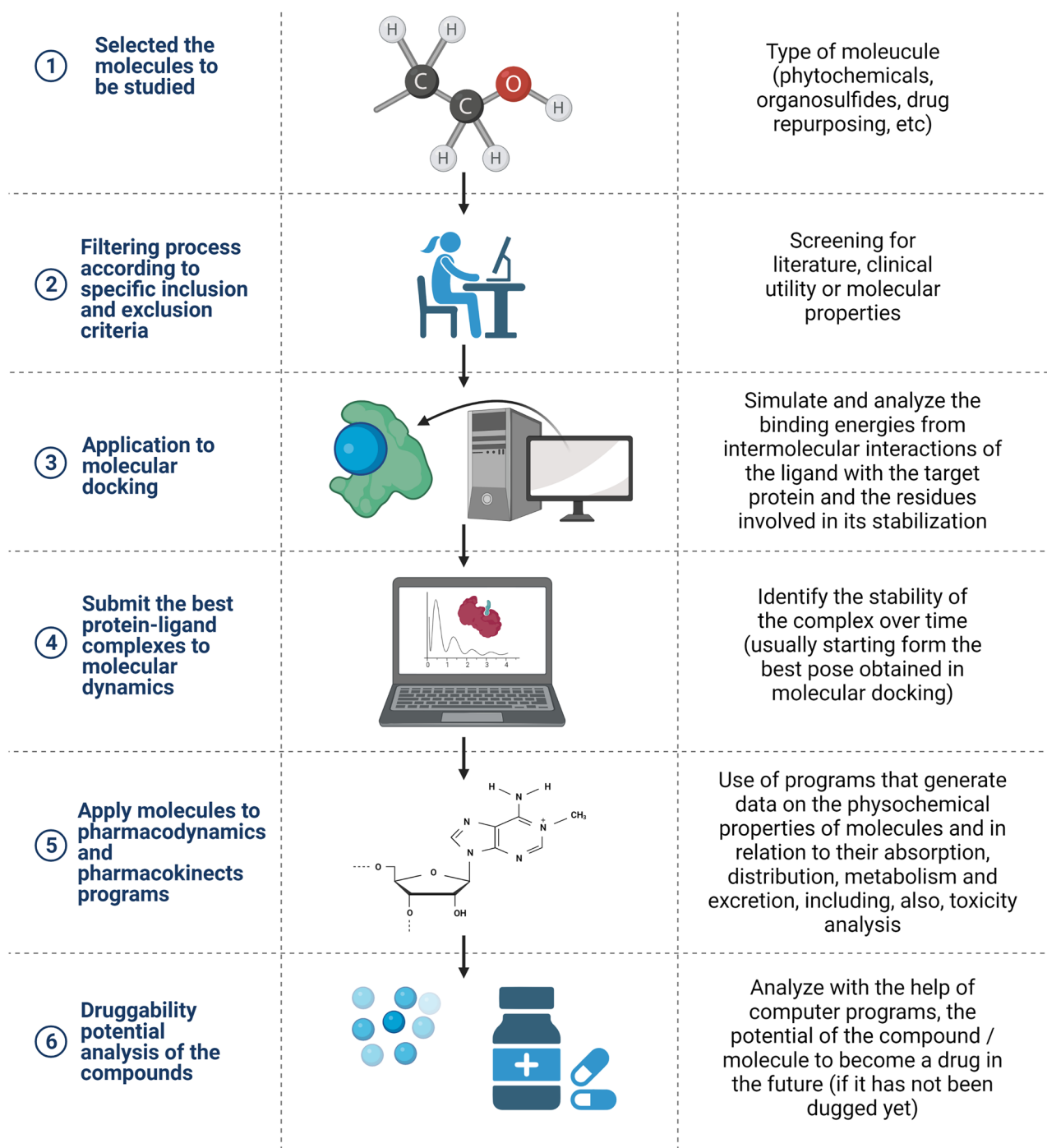


Fig. 2 Representation of the standard experimental design used in the articles

same way, Morin, a flavonol found in several herbs that has potential antiviral action, was found to have good binding energy and the molecule obeys Lipinski's rule of five. However, despite the good absorption and permeability

through the gastrointestinal tract, Morin may present mutagenic effects (Gupta et al. 2021).

Other PLpro activities, such as deubiquitination and deISGylating activities, also appear as a target for in silico

Table 1 This table presents the works which were not included in the text

<i>Literature</i>	<i>Highlights</i>	<i>DOI code</i>
Li et al. (2021)	Neobeavaisoflavone showed the higher free energy, followed by oseltamivir	https://doi.org/10.1016/j.bbrc.2020.11.083
Tan et al. (2020)	Oseltamivir is not effective in the treatment of COVID-19 (in silico, in vitro tests, and case reviews)	https://doi.org/10.1016/j.bioorg.2020.104257
Quimque et al. (2020)	Scedapin C and quinadoline B exhibited the highest binding affinities for PLpro, 3CLpro, RdRp, and nsp15	https://doi.org/10.1080/07391102.2020.1776639
Ibrahim et al. (2020)	Perfenazine, benserazide, and isocarboxazide were the best classified drugs for the three structures used	https://doi.org/10.3389/fchem.2020.592289
Thurakkal et al. (2021)	Lurasidone sulfoxide and lurasidone endo were the best placed molecules in the molecular docking with PLpro	https://doi.org/10.1016/j.cplett.2020.138193
Nejat and Shahir (2021)	Imatinib has a high binding affinity with PLpro and losartan can act in the conformational form of the protein	https://doi.org/10.1007/s40203-020-00058-7
Naidoo et al. (2020)	Cryptophycin 1, cryptophycin 52, and deoxycylindrospermopsin exhibited the best binding energies regarding PLpro	https://doi.org/10.1080/07391102.2020.1794972
Cavasotto and Di (2021)	Anatibant, Pilaralisib, Zabofoxacin, Tiracizine, Picotamide, BMSC-0013, Darolutamide, Cilazapril, Indisulam, Ziprasidone, and Propadimine are shown to be potential inhibitors for PLpro	https://doi.org/10.1002/minf.202000115
Kouznetsova et al. (2020)	Nilotinib had the lowest binding free energy	https://doi.org/10.7717/peerj.9965
Kandeel et al. (2020)	Phenformin, quercetin, and ritonavir showed the best performance in MD simulation and MM/GBSA binding energy calculations	https://doi.org/10.1080/07391102.2020.1784291
Amin et al. (2020)	The IH-009 compound presented the best interaction, forming 3 hydrogen bonds (LEU162, TYR264, and TYR268) and π - π T-shaped and π -alkyl interactions	https://doi.org/10.1080/07391102.2020.1780946
Bosken et al. (2020)	The naphthalene-based compound, 3 k (SARS-CoV inhibitor), had the strongest potential to inhibit the SARS-CoV-2 PLpro and this was confirmed in experimental assays	https://doi.org/10.3389/fmolb.2020.00174
Elekofehinti et al. (2020)	STOCK1N-69160, STOCK1N-68604, and STOCK1N-66718 emerged as potential inhibitors of the PLpro considering their docking scores	https://doi.org/10.1007/s11030-020-10151-w
Khanal et al. (2020)	Torososide B presented the highest binding affinity (– 8.7 kcal/mol) and formed 9 hydrogen bonds with PLpro	https://doi.org/10.1007/s13659-020-00260-2
Ranjbar et al. (2020)	RV-13 derivative presented the best binding energy (– 184.99 kJ/mol) and formed hydrogen bond, Van der Waals, Pi-sigma, and doner-doner interactions with PLpro	https://doi.org/10.26355/eurrev_202007_22288
Murugan et al. (2020)	Natamycin and lumacaftor showed lower binding energies	https://doi.org/10.1038/s41598-020-75762-7
Rabie (2021)	The binding energies of CoViTris2020 and ChloViD2020 against PLpro were – 10.60 and – 9.30 kcal/mol, respectively, and they were able to inhibit the virus replication in Vero E6 cells. Also, both can strongly bond with zinc atoms and affect the virus replication	https://doi.org/10.1007/s11030-020-10169-0
Rajpoot et al. (2021)	ZINC 389,747, ZINC 1,530,637, and ZINC 49,153 form stable complexes with Mpro and PLpro in the MD simulation	https://doi.org/10.1016/j.crstbi.2020.12.001
Bhati (2020)	LigandL10 formed a stable complex with the SARS-CoV-2 PLpro	https://doi.org/10.1016/j.heliyon.2020.e05558
Chen et al. (2021)	The authors created a new database only for the SARS-CoV-2 with FDA-approved drugs and from the National Health Insurance (NHI), from Taiwan	https://doi.org/10.1093/nar/gkaa861
AlAjmi et al. (2020)	R2 had the lowest binding energy and binds in the binding site of the PLpro, forming 5 hydrogen bonds in the MD simulation; it formed a stable protein-inhibitor complex	https://doi.org/10.1080/07391102.2020.1799865

Works that were selected based on the search for the following keywords: “in silico”+“COVID-19”+“papain-like protease” and “docking”+ “COVID-19”+ “papain-like protease,” but the results were not included in the text. The search provided 17 articles for the first keyword list and 37 for the second. The exclusion criteria included the existence of replicates between the lists, the review articles, articles in other languages than English, and articles that are unavailable to the general public or those without access permission for our educational institution

research. The carboxyl terminal hydrolase of human ubiquitin 2 (USP2), which acts on the growth suppression of cancer cells addicted to the expression of cyclinD1, is an important regulator in the progression of the cell cycle (Shan et al. 2009). This protein shares a similar structure with PLpro and hydrolyzes ubiquitin types (Báez-Santos et al. 2015). After pharmacokinetic screening, Mirza et al. (2020) applied already known antagonists and inhibitors for USP2 to molecular docking with PLpro. The ones that had the best binding energies were subjected to in vitro tests. The antagonist Z93 derivative showed better interactions when complexed with PLpro as compared to the complex formed with USP2; therefore, it may act as an inhibitor of its deubiquitination activity (Mirza et al. 2020).

Bioactive nutraceuticals derived from the diet were also studied (Mhatre et al. 2021), more specifically Epigallo catechim gallate (EGCG) and Theflavin digalatte (TF3), which are polyphenols derived from green and black teas, respectively. These compounds showed to have little brain-blood barrier permeability, but good intestinal absorption and absence of hepatotoxicity (Mhare et al. 2021). In addition, results obtained in the molecular docking for EGCG and TRF3 with PLpro were inferior to -8 kcal/mol, having amino acids in common interacting through hydrogen bonds (Mhatre et al. 2021). Nevertheless, they also do not interact with the catalytic site itself. On the other hand, in a study focused on the ubiquitination activity of PLpro, the compound EGCG, together with cyanidin-3-O-glucoside, rutin, and hypericin, showed a strong binding affinity with the residues involved in the stabilization of known PLpro inhibitors (GRL-0617 and 3 k). All four compounds showed better binding energies when compared to the controls on PLpro deubiquitination and disISGylation activities. Hypericin also presented the greatest potency in inhibiting protease in vitro when comparing to the other four compounds, from a dose-dependent perspective, and rutin presented the best binding energy in the in silico analysis (Pitsillou et al. 2020b). Rutin is the main phytoconstituent of *Azadirachta Indica* (Juss 1832) and acts as an antioxidant, also showing antiprotozoal, antibacterial, and antiviral properties (Ganeshpurkar and Saluja 2017). In addition, it is already known that it can act as a protease inhibitor, for example, in norovirus and enterovirus (Chéron et al. 2015; Lin et al. 2012). Nevertheless, the flavonoid showed good binding at the PLpro catalytic site and can be a potential inhibitor of Mpro (major serine-like protease) and RdRp (RNA-dependent RNA polymerase), also presenting hydrogen bonds and a hydrophobic interaction in the catalytic site of the spike protein (Rahman et al. 2021a). The interactions of Rutin with PLpro allow that the final molecule may inhibit viral replication by disrupting the signaling cascade of infected cells. Furthermore, pharmacokinetic tests have shown good solubility

and absence of toxicity and carcinogenic action (Rahman et al. 2021a). Considering all compounds above discussed, Rutin seems to present the best potential to inhibit the PLpro in vivo, corroborating with its neuroprotective, vasoprotective, cytoprotective, anticarcinogenic, cardioprotective, and antioxidant properties already identified (Ganeshpurkar and Saluja 2017).

Vardhan and Sahoo (2020) selected limonoids and triterpenoids for several in silico analyzes, including molecular docking, ADMET, and drug similarity prediction. Among them, glycyrrhizic acid showed a great binding energy when it binds to the catalytic triad in the active site of PLpro. Other phytochemicals such as obacunone, ursolic acid, and 7-diacetylgedunin also showed a connection with the site. However, glycyrrhizic acid was the only one to show good results for all other proteins tested (RdRp, S, ACE2, Mpro) (Vardhan and Sahoo 2020). In addition, this herbal derivative was presented as one of the potential compounds in the treatment of SARS-CoV-2, acting on PLpro and Mpro in a review of in vivo, in vitro, and in silico studies. This compound presents antiviral activities against infection and inflammation, as well as specific properties regarding the inhibition of SARS-CoV-2. Its role in inflammation has been speculated about the possibility of a beneficial effect of the molecule in relation to the cytokine storm triggered by the viral infection (Remali and Aizat 2021). Thus, glycyrrhizic acid is another good candidate to inhibit the SARS-CoV-2 infection.

Furthermore, derivatives from different parts of the herbal plant *Vitex negundo* (AFPD 2008) were submitted by Mitra et al. (2021) to in silico tests with PLpro. Four molecules stand out: oleanoic acid, followed by ursolic acid, 3 β -acetoxyolean-12-acid in-27-oic, and isovitexin. The study showed that all compounds have low gastro-intestinal absorption and as to toxicity, it showed that the oleanoic acid, ursolic acid, and 3 β -acetoxyolean-12-acid in-27-oic belong to class four of toxicity, whereas the isovitexin is classified as class three. Based on this, the authors suggest more studies using isomers that may have better pharmacokinetic properties to inhibit this protease (Mitra et al. 2021).

Besides, in a substantial study that evaluated the pathways involved in the pathophysiology of COVID-19 and possible treatment targets, the derivatives of anthroquinones and glycosides, lupeal and quercetin, had the best docking results, showing great binding energies (Fatoki et al. 2020). Anthraquinone derivatives, frequently used in the Ayurvedic system, resveratrol, that are polyphenols with several pharmacological and bio-functional activities, such as antiviral, anticardiovascular, and antioxidant properties, and other natural compounds were also retrieved for virtual screening with the PLpro (Ranjbar et al. 2020; Khanal et al. 2020; Olalekan et al. 2020).

Briefly, the repurposing of drugs used in other diseases with symptoms similar to that of COVID-19 is another interesting strategy used by many researchers to discover potential PLpro inhibitors (Cavasotto and Di 2021; Quimque et al. 2020; Kandeel et al. 2020; Delre et al. 2020). The compound VIR251 is a PLpro inhibitor widely used for validation of methodologies and binding comparison (Kandeel et al. 2020; Delre et al. 2020). In this way, the specific type of binding between PLpro CYS111 and VIR251 was used as a selection criterion for covalent protease inhibitors, some of them being phytochemicals (Delre et al. 2020). Only two compounds showed the ability to reproduce the binding mold of VIR251, afatinib, and curcumin, the last being a natural compound that presented the best molecular docking score, in addition to performing key interactions similar to the standard inhibitor. This molecule is a derivative of *Curcuma longa* (Flora of China Editorial Committee 2000) that has already been reported to exert anti-inflammatory actions on the gastrointestinal, cardiovascular, and hormonal systems, and even against microorganisms (Ammon and Wahl 1991), presenting antifungal, antibacterial, and antiviral activities (Moghadamtousi et al. 2014). Curcumin also has beneficial effects on Alzheimer disease (Reddy et al. 2018; da Costa et al. 2018; Tiwari et al. 2014). With such interesting neural actions, it is a good candidate to inhibit the SARS-CoV-2 infection (Delre et al. 2020).

Recent Developments: In Vitro and In Vivo Experiments

Although data above presented are encouraging, there is no proof of effectiveness, either in vitro and/or in vivo, in relation to PLpro for most of the compounds. However, some molecules, or their derivatives, were subsequently analyzed or submitted to evaluation against other viral proteins or the virus itself. Withanolides, a product of the plant *Withanolide somnifera*, were drilled to in silico tests by other groups in combination with in vitro, using human cancer (A549, MCF7, and HSC3) cells (Kalra et al. 2021), and in vivo analysis in a humanized zebrafish model (Balkrishna et al. 2021). Withanolide B, despite being present in the studies, was not selected for testing. Epigallo catechin gallate (EGCG) has been shown to inhibit the infection of SARS-CoV-2 and even of SARS-CoV and MERS-CoV in HEK293T-ACE2, Vero, and Huh7 cells (Henss et al. 2021). Furthermore, it can act against the human coronavirus (HCoV OC43) and its new variants (UK-B.1.1.7, SA-B.1.1.351, and CA-B.1.429) in human lung epithelial cells (Calu-3) and HEK293-hACE2 cell (Liu et al. 2021). It also inhibited the activity of 3CLpro, another viral protein involved in proteolytic activities, in HEK293T human embryonic kidney cells (Jang et al. 2020). The action of EGCG on viral replication and contact

of ACE2 with the spike protein was also described (Joseph et al. 2021), being the affinity of EGCG for the spike protein the main factor that explains its inhibitory action (Tsvetkov et al. 2020). Moreover, it has an inhibitory potential against uridylate-specific endoribonuclease Nsp15, involved in viral RNA processing (Hong et al. 2021). Interestingly, the virus has been shown to be inactivated in human saliva by green tea and black tea (Ohgitani et al. 2021), from which respectively derive EGCG and Theflavin digalatte (TF3), a compound that was previously discussed.

Another promising compound in the inhibition of PLpro is Cyanidin-3-O-glucoside (Pitsillou et al. 2020c) that, together with hypericin, has been subjected by the same group to in vitro validations and in silico studies in relation to the Mpro (Pitsillou et al. 2020a; Liang et al. 2020). Inhibitory potential of these compounds on the enzymatic activity of PLpro has been reported; hypericin has an inhibitory effect dose-independent, while Cyanidin-3-O-glucoside and rutin are dose-dependent inhibitors (Pitsillou et al. 2020c). Rutin, in addition to promising results for PLpro, binds to the catalytic site of 3CLpro and has an inhibitory effect with $IC_{50} = 32 \mu M$ in *Escherichia coli* (*E. coli*) cells expressing the SARS-CoV-2 3CLpro (Rizzuti et al. 2021). Another group described an $IC_{50} = 31 \mu M$ and important anti-inflammatory effects for rutin and other *Pimenta dioica* derivatives in Vero E6 cells and Albino rats, corroborating the compound's potential (El Gizawy et al. 2021). As for hypericin, the drug's inability to inhibit Mpro in vitro was also reported in *E. coli* cells expressing the protein (Keutmann and Olagunju 2020).

Glycyrrhizinic acid has been shown to inhibit SARS-CoV-2 and to be able to reduce viral RNA in Vero E6 cell culture, although it acts potentially in the Mpro (Sand et al. 2021). Besides, treatment with *Glycyrrhiza glabra* (Hickman 1993), the plant that the compound is derived, has been shown to reduce ACE2 expression in the intestine of rats, at mRNA and protein levels (Jezova et al. 2021). It is known that SARS-CoV-2 infection may be linked to activation of Toll-like receptors, which promote an inflammatory response mainly in macrophages; as demonstrated by Dosch and colleagues, the virus S protein can lead to the production of IL-8 mediated by TLR-2, ubiquitously expressed in this cell line (Dosch et al. 2009). In this perspective, glycyrrhizinic acid in RAW264.7 cell line incubated with LPS significantly reduced the release of interleukin-6, an important cytokine in COVID-19 (Yang et al. 2020). In view of its promising results, testing the inhibition of PLpro in vitro by the compound would be interesting, since it acts on Mpro, in the ACE2 expression, and on inflammation, characterizing a potential drug for the treatment of COVID-19. In addition, nanoparticles containing the substance were able to inhibit MHV-A59 (murine hepatitis virus, strain A59) replication and reduce hyperinflammation, in vitro (L929 cells) and in vivo (mice model), being a technology that could help in the treatment of COVID-19 (Zhao et al. 2021).

Quercetin and curcumin were able to block viral replication in Vero E6 cells (Kandeil et al. 2021), and organoselenic derivatives of quercetin also demonstrated antiviral activities (Mangiavacchi et al. 2021). In addition, its supplementation at the onset of SARS-CoV-2 infection is associated with reduced oxygen use and length of hospital stay (Pierro et al. 2021). Curcumin, as discussed before, has antiviral action (Kandeil et al. 2021) and this activity extends to variants such as delta (Mar et al. 2021); such effect showed up in Vero E6 and human Calu-3 cells and in several forms, including natural extract, supplemented capsules, and purified substance (Bormann et al. 2021). In addition to being suggested as a PLpro inhibitor, curcumin is a promising Mpro inhibitor, with in vitro activities on the enzyme (Guijarro-Real et al. 2021). Furthermore, treatment with nano-curcumin was able to modulate the inflammatory effects of COVID-19 in patients, including downregulation of IL-6 and IL-1B, important hallmarks of the cytokine storm described for the disease (Valizadeh et al. 2020). Nano-curcumin significantly reduce Th17 cells and associated pro-inflammatory effects, in addition to increasing Treg cell expression and, consequently, their related anti-inflammatory activities in COVID-19 patients (Tahmasebi et al. 2020, Tahmasebi et al. 2021). In addition, curcumin has shown beneficial effects in clinical trials (Ahmadi et al. 2021; Hassaniyazad et al. 2021) and, in combination with piperin, has been suggested to mitigate the symptoms of COVID-19 (Pawar et al. 2021).

Although several compounds cited present a potential treatment for COVID-19, most of them were not tested in preclinical and clinical studies. These are fundamental for use evaluation in humans because, several times, even compounds that demonstrate pharmacological action in vitro and in silico assays are disapproved in subsequent studies regarding efficacy and safety. Table 2 provides recent literature on other compounds that were not discussed in this section.

COVID-19 in the SNC: Lessons from Alzheimer's Disease Research?

The neuropathology of Alzheimer's disease involves tissue accumulation of beta amyloid, deposition of beta amyloid plaques, and the intracellular presence of neurofibrillary tangles derived from the tau protein; a cytoskeleton protein associated with microtubules. However, it is already known that neuropathological mechanisms are a lot more complex (Ballard et al. 2011).

It is known that SARS-CoV-2 infection generates neurological manifestations (Whittaker et al. 2020; Montalvan et al. 2020). Even though it has been reported that approximately 36% of patients exhibit neural symptoms

(Mao et al. 2020) and that the presence of viral particles in the central nervous system (CNS) has been confirmed (Moriguchi et al. 2020), the mechanism by which the virus infects the CNS has not been determined. Two possibilities have been put forward: one is that the virus invades the brain through circulation, infecting cells that exhibit ACE2 in other body regions, such as the lungs, and thus travels through the bloodstream and reaches brain fluid (Baig et al. 2020). Another hypothesis is that the virus arrives to the brain through the olfactory bulb (Netland et al. 2008). In this perspective, it is important to observe the permeability of drugs to the brain-blood barrier in the treatment of COVID-19 and neurodegeneration (Fig. 3).

Moreover, Chen and colleagues reported that PLpro, more specifically its transmembrane domain (PLpro-TM), can trigger negative immune regulation in the host via a signaling pathway that activates interferon type I transcription. They observed that, in the presence of PLpro-TM, the complex responsible for activating IRF3 that triggers the transcription of the inflammatory mediator is disrupted (Chen et al. 2014). This complex, consisting of the STING-TRAF3-TBK1 proteins, once corrupted, results in the non-induction of TBK1 by TRAF3, responsible for dimerizing and phosphorylating IRF3 (Fitzgerald et al. 2003). Also, due to its deubiquitination activity, PLpro reduces the levels of ubiquitination of several inflammatory mediators involved in interferon signaling (Chen et al. 2014). Therefore, IRF3 does not translocate to the nucleus, the interferon is not expressed and mediators such as TBK1, dissociated from the complex, are unobstructed. Interestingly, TBK1 has been shown to directly phosphorylate the Tau protein, leading to its hyperphosphorylation (Abreha et al. 2021). Tau protein is responsible for the stability of microtubules under normal conditions; however, when hyperphosphorylated, it forms neurofibrillary tangles (NFT), a hallmark of Alzheimer's disease (Alonso et al. 1994; Bancher et al. 1989). Abreha and colleagues reported that Tau is a substrate for TBK1, and its overexpression is linked to high rates of hyperphosphorylated Tau, while in knockdown animals for TBK1 there is hypophosphorylation of this protein (Abreha et al. 2021). It is known that pathological effects on neuronal cells and their synapses are often linked to hyperphosphorylated Tau (Augustinack et al. 2009). In general, TBK1 protein is very important to the immune response, especially to infections, as it participates in the signaling of inflammatory pathways (Perry et al. 2004, Marchlik et al. 2010). SARS-CoV-2 triggers an immune response; however, the mechanism demonstrated by Chen et al. (2014) suggests a negative regulation of the effects of this response and favors infection. Therefore, TBK1, when dissociated from the complex, does not phosphorylate IRF3, being free to act on other proteins. Thus, in individuals with tauopathies, such as AD, the infection can contribute to Tau hyperphosphorylation and the formation

Table 2 Recent in vitro, in vivo, and clinical trial literature of molecules that were not included in the text

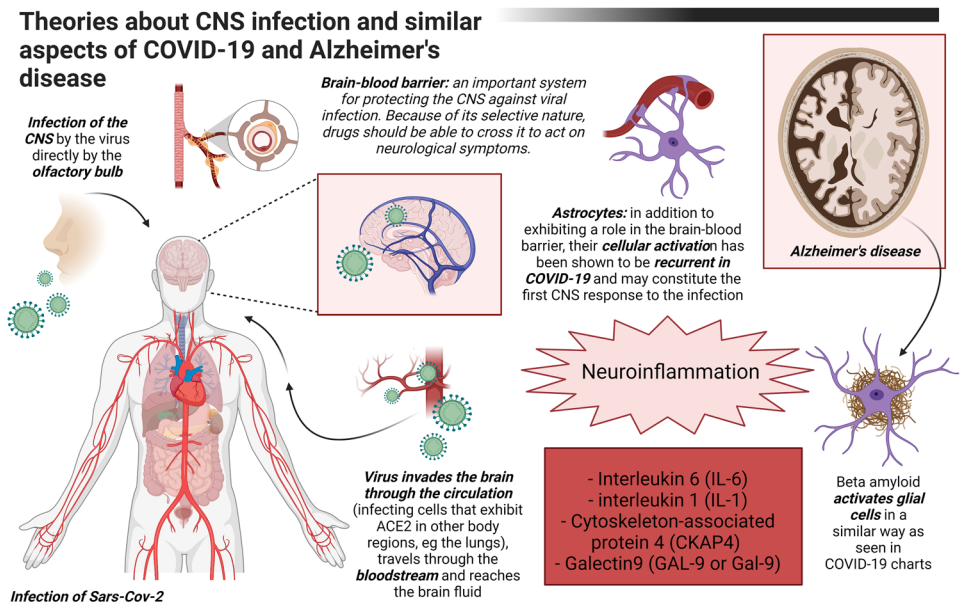
<i>Compound</i>	<i>Main findings</i>	<i>Reference</i>
In vitro		
Compound		
Hypericin, lurasidone, desatinib	Enzyme-based fluorescence assay	Hypericin fails to inhibit Mpro. Lurasidone and desatinib were able to inhibit the enzyme effectively and partially, respectively
Lurasidone	Huh7 cells carrying the human ACE2 receptor	Lurasidone showed an antiviral profile against SARS-CoV2
Nilotinib	Vero E6 cells Vero-E6 cells and Calu-3 cells	Showed antiviral potential Interfered with the replication of SARS-CoV-2 in both cell lineages
Imatinib	VeroE6 cells and human airway epithelia (HAE) Naturally susceptible ACE2+ human Caco-2	Inhibited SARS-Cov-2 replication, but it not showed significant antiviral activity at HAE Cells have no significant effect on SARS-CoV-2 infection and replication
Spiroinolactone	HEK-293 T, MDA-MB-231, Calu3, Vero E6, HCASMC, 16HBE14o co-transfected with ACE2 receptor Primary human aortic endothelial cells exposed to androgens	Inhibited the RNA and protein expression of ACE2 in multiple cell lines Reduced endothelial injury by S1 in the presence of DHT or TNF- α in vitro. Reduced ACE2 transcript expression in ECs
Remdesivir and galidesivir	Vero E6, human hepatoma (Huh7 and Huh7.5), HEK-293 T, BHK-21, and Calu-1 cells	Showed antiviral effects across human cell lines
Remdesivir	HAE, Calu3 2B4, and Vero E6 cells VERO E6 cells	Potently inhibits SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures, with lower activity in Vero E6 cells Used in association with PLpro inhibitors to facilitate their action on the enzyme, but not reduce the EC50 of the tested compounds
Lumacaffor	Vero and human 293 T cells expressing the ACE2 receptor	Cobinated with PLpro inhibitors could potentially have an antiviral activity against SARS-CoV-2. This does not occur with those compounds that only inhibit Mpro
Ritonavir	Vero-E6 cells Vero cells	Demonstrated dose-dependent antiviral action Reduced cytopathic effects and viral load
Losartan	Vero E6 cells and inhibition of Poly-Ub and proISG15 Cleavage	Prevented SARS-CoV-2 replication and showed a low inhibitory potential on viral PLpro deubiquitinating and desigilimating activities
In vivo	Primary human endothelial and human pluripotent stem cell-derived cardiomyocyte	Did not change the viral load or ACE2 expression levels
Compound		
Imatinib	Syrian hamsters	Showed good penetration in the lungs, but it is incapable to prevent viral replication in the model
Remdesivir	Rhesus macaques Clinical trials	Reduced clinical disease and damage to the lungs

Table 2 (continued)

<i>Compound</i>	<i>Main findings</i>	<i>Reference</i>
In vitro		
Imatinib	A randomized, double-blind, placebo-controlled, clinical trial	Aman et al. (2021)
Spirolactone	A randomized HOMAGE (Heart OMics in AGEing) clinical trial	Ferreira et al. (2021)
	Nationwide case-control study on liver cirrhosis patients	Jeon et al. (2021)
Remdesivir	Randomized, double-blind, placebo-controlled, multicentre trial	Wang et al. (2020)
Ritonavir (tested with lopinavir)	Randomized, controlled, open-label trial involving hospitalized adult patients	Cao et al. (n.d.)
	Randomized controlled trial of critical patients	Arabi et al. (2021)
	Open-label, randomized, phase 2 trial	Hung et al. (2020)
Losartan	Patients hospitalized with SARS-CoV-2 infection	Bolotova et al. (2020)
	Open-label non-randomized trial. Trial in hospitalized with COVID-19	Bengtson et al. (2021)
	Open-label randomized controlled trial	Geriak et al. (2021)

In vitro, in vivo, and clinical tests on compounds that were not included on the main text of the review

Fig. 3 Synthesis of the theories that permeate the infection of the CNS. The infection through the olfactory bulb on the left, next to the proposed infection via circulation. In the sequence, a blood barrier is displayed in the upper central part, followed by the representation of the astrocytic presence in the barrier. On the right follows a comparison with astrocyte activation identified in Alzheimer's disease, related to the accumulation of beta amyloid. Finally, the main inflammatory markers present in both pathologies stand out



of NFTs and, consequently, amplify the brain damage seen in these diseases.

Another similarity between SARS-CoV-2 infection and Alzheimer's disease is the evidence of mitochondrial disorders related to the presence of inflammation and, in the case of AD, to the accumulation of beta amyloid. This characteristic was reviewed by several authors associating aspects of aging and other comorbidities (Tobore 2019; Wang et al. 2014; Shenoy 2020). Furthermore, the pathology of COVID-19 was associated with mitochondrial dysfunction in monocytes, directly depleting cell energy generation (Gibellini et al. 2020).

Nevertheless, since the microbiota has regulatory power over the immune system (Chung et al. 2012; Sassone-corsi et al. 2022), it may influence responses to infectious and neurodegenerative diseases. Interestingly, changes in the microbiota were reported in both COVID-19 and Alzheimer's disease patients. In COVID-19 patients, a decrease in the concentration of the *Eubacterium rectale* strain was observed (Yeoh et al. 2021). Curiously, the same was found in patients with DA and/or cognitive impairment (Cattaneo et al. 2017). In both diseases, the concentration of inflammatory molecules is increased; levels of inflammatory biomarkers are inversely related with the presence of the *E. rectale* strain. In this way, microbiota disruption unveils another similarity between both diseases.

There is also the hypothesis that, in moderate to severe cases of COVID-19, there is great activation of astrocytes, thus constituting one of the first responses of the CNS to the infection (Kanberg et al. 2020). In addition, astrocytes play a key role in maintaining the brain-blood barrier (Engelhardt and Coisne 2011), being these cells related to CNS infection. In Alzheimer's disease, amyloid beta is known to activate

glial cells (Holmes and Butchart 2011) and, furthermore, curcumin has shown potential to reduce such activation in vitro (Shi et al. 2015). Besides, in pre-clinical studies, the phytochemical decreases inflammatory cytokines in Alzheimer's disease (Liu et al. 2016) and shows protective effects against accumulated beta amyloid, presenting behavioral and neurotoxicity improvements through dietary supplementation (da Costa et al. 2018). In addition, curcumin is associated to neurogenesis and improvement on cognitive performance in adult rats (Tiwari et al. 2014).

Interestingly, there are several common inflammatory markers between COVID-19 and Alzheimer's disease, such as interleukin 6 (IL-6), interleukin 1 (IL-1), protein 4 associated with the cytoskeleton (CKAP4), and galectin9 (GAL-9 or Gal-9) (Rahman et al. 2021b). Thus, curcumin is an interesting molecule as regards to repurposing of drugs for the treatment of COVID-19.

Glycyrrhizic acid is a natural product found in the roots of *Glycyrrhiza glabra L.* ("licquorice" or "licorice") widely used in Chinese medicine. Regarding pre-clinical studies, glycyrrhizic acid has already been shown to prevent cognitive deficits and neuroinflammation in rodents treated with lipopolysaccharide, in addition to promoting glial cell activation (Song et al. 2013). Nevertheless, it reduced Tau phosphorylation in the hippocampus of aged mice, as well as decreased the nuclear expression of NF- κ B and the production of pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 (Kong et al. 2017). Furthermore, the diammonium glycyrrhizinate salt suppressed the microglial activation in in vitro and in vivo models, and this activity may be related to the MAPK and NF- κ B pathways (Zhao et al. 2013). In in vitro and in silico studies, glycyrrhizic acid has shown anti-inflammatory activities that inhibit the mitogenic

activities of high mobility group 1 box protein (HMGB1), a protein active in the regulation of inflammation (Mollica et al. 2007). In this way, it is also related to a positive effect on HMGB1-mediated neurological disorders and the possibility of successful clinical treatment (Paudel et al. 2020). In clinical studies, its use appears to be beneficial in the treatment of depression (Cao et al. 2020) and the oral administration of its precursor, licorice, ameliorates Parkinson's common symptoms (Petramfar et al. 2020). Moreover, glycyrrhizinic acid is suggested as a potential drug for COVID-19 based on its effects in relation to similar diseases, such as pulmonary disease and the human immunodeficiency virus 1 (HIV-1) infection (Bailly and Vergoten 2020).

Curcumin and Glycyrrhizinic Acid-Related Benefits

Authors have associated curcumin to oxidative stress in association with mitochondrial functioning and a bidirectional relationship with gut microbiota, since it favors bacterial strains and can be metabolized by certain species (Scazzocchio and Minghetti 2020; Di Meo et al. 2019). This molecule can act on reactive oxygen species and control apoptosis via Bcl-2 proteins (Pongrakhananon and Nimmannit 2010), in addition to reducing dose-dependent oxidative stress associated with increased activity of antioxidant enzymes such as superoxide dismutase (SOD) (Alizadeh and Kheirouri 2019). Interestingly, Alzheimer's disease model mice treated with curcumin showed a normalization of the gut microbiota, accompanied by an improvement in memory and spatial learning and a reduction in the accumulation of amyloid plaques (Sun et al. 2020). Besides, Sun and colleagues reported similar positive effects of curcumin metabolites on this process. These metabolites are also associated with neuroprotection against oxidative stress and beta amyloid in Alzheimer's disease models and in vitro assays (Ahmed et al. 2010; Pinkaew et al. 2015).

Similar to curcumin, glycyrrhizinic acid showed a neuroprotective effect in the treatment of chronic cerebral hypoperfusion in rodents (Sathyamoorthy et al. 2020), being able to exert antioxidant actions in addition to increasing GSH levels. In the same study, the treatment with this compound was associated with decreased expression of Tau, a protein usually related to several neuropathologies, including AD. In addition, it reestablishes complexes I and IV of the respiratory chain, probably by preventing the formation of reactive oxygen species. Glycyrrhizinic acid was also related to increase expression of anti-apoptotic Bcl-2 proteins and, concomitantly, reduction of Bax proteins and caspase 3 levels in a rodent model of vascular dementia (Sathyamoorthy et al. 2020). Another study showed that GA-related compounds, glycyrrhizin and 18 β -glycyrrhetic acid, have similar actions such as suppressing ROS formation, GSH modulation, and preventing mitochondrial permeability (Lee et al. 2007). Moreover, glycyrrhizinic acid was related to the

intestinal microbiota in rodent models, since its levels in blood and plasma were affected by antibiotics that act on the bacteria of the intestinal microbiota (Ishida et al. 2022), indicating that the microbial composition of the gastrointestinal tract influences the pharmacokinetics of the compound. In the arterial system, endothelial cells submitted to ischemia/reperfusion and hypoxia/reoxygenation, glycyrrhizinic acid was able to prevent the collapse of mitochondrial membrane potential and to restore ATP production. The authors evidenced other benefits, including the reduction of ROS accumulation following ischemia (Tang et al. 2020).

In addition to curcumin and glycyrrhizinic acid, there is evidence that other small molecules may act upon COVID-19 and AD; however, it would be impossible to cover the whole list of molecules in this brief paper. Therefore, we chose to highlight curcumin and glycyrrhizinic acid because, in addition to their PLpro inhibitory effects, they favor the evidence of the similarities of neurological manifestations between COVID-19 and neurodegenerative disorders, such as AD.

Conclusion

There is plenty in silico studies of small molecules related to the viral proteins of SARS-CoV-2. In this review, we highlighted the search for inhibitors of PLpro, one of the proteases active in viral replication, which also has deubiquitination and deISGylation functions that are currently targeted in many tests. Some similarities between Alzheimer's disease and COVID-19, as regards to inflammation and phytochemicals that bear potential of therapeutic actions, curcumin and glycyrrhizinic acid, have been discussed since in silico studies involving these herbal derivatives have shown good PLpro inhibitory activities. Finally, this article shows the similarities between the effects of SARS-CoV-2 infection on the brain and neurodegenerative disorders. Therefore, it can help future work in the area.

Author Contribution ASR was responsible for roles/writing – original draft, writing – review and editing, and design and creation of figures; BFD helped in writing; CAN was responsible for funding acquisition, project administration, resources, and writing – review and editing; ATSW was responsible for conceptualization, funding acquisition, project administration, resources, supervision, and writing – review and editing.

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Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Competing Interests The authors declare no competing interests.

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