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Research Article

In silico phytochemicals analysis as inhibitors of the SARS-COV-2 main protease

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Abstract

Background: The world population's full immunization with vaccines against SARS-CoV-2 is still challenging. Therefore, more research must be needed to find an active antiviral drug against the virus, including new mutated strains.

Results: Therefore, this research analyzes 35 natural compounds isolated from various plants against SARS-CoV-2 main protease (Mpro) using an *in silico* strategy. According to the results, it was possible to identify promising molecules using a molecular docking strategy. Furthermore, the results showed that the interaction of these molecules with protease-specific residues, including (2S)-Eriodictyol 7-O-(6"-O-galloyl)-beta-D-glucopyranoside (Trp207, Ser284, and Glu288), Hypericin (Glu166, Arg188, and Thr190), Calceolarioside B (Gly143, Ser144, Cys145, Glu166, Arg188, and Gln192), Epicatechin (Ser144, His163, and Leu167) and Myricitrin (Thr190) with ΔG was -8.5, -9.6, -8.5, -9.3 and -9.3 kcal/mol, respectively. In addition, analyzing all compounds for their ADME properties shows that compounds present an excellent pharmacokinetic profile.

Conclusion: In conclusion, the results of this study indicated that these major natural compounds can be considered potential inhibitors of Mpro and should be further explored *in vitro* and *in vivo* in accordance with our data.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; Mpro: Main protease; ADME: Absorption, Distribution, Metabolism, and Excretion; Trp: Tryptophane; Ser: Serine; Glu: Glutamic acid; Arg: Arginine; Thr: Threonine; Gly: Glycine; Cys: Cysteine; Gln: Glutamine; Leu: Leucine; ΔG: Gibbs free energy; kcal: kilo calories; mol: mole; VOC: Variants of Concern; MMFF94: Merck Molecular Force Field 94; 3D: Three Dimensional; PDB ID: Protein Data Bank Identification; mol2: portable representation of an SYBYL molecule; SMILE: Simplified Molecular-Input Line-Entry System; FDA: U.S. Food and Drug Administration; ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; Å2: Variation of the mean accessible surface area; H-bond: Hydrogen bond; logP: logarithm (base 10) of the partition coefficient P; Log Po/w: Logarithm (base 10) of the octanol/water partition coefficient

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Background

Although many countries have reviewed restrictive measures and have relaxed the use of masks [1], some countries do not have a fully immunized population. This scenario could highlight the middle- or low-income countries with few resources to acquire the developed immunizers and lack donations from richer countries [2,3]. In addition, in some countries, the population is waiting for newer vaccine applications as a booster against COVID-19 [4-6]. When the pandemic started, pharmaceutical enterprises suggested several drugs as treatments. However, they presented significantly less effectiveness than previous data suggested in clinical trials [7]. In addition, coronavirus can rapidly mutate, which may demand new effective vaccines shortly [8].

In this context, the identified variants have elevated the race for new drugs and vaccines against important VOC, such as alpha (B.1.1.7), beta (B. 1.351), gamma (P.1), and delta (B. 1.617.2). Moreover, the low vaccine adherence in several countries promoted the development of new variants. This scenario is the case of the omicron Variant (B.1.1.529), whose dissemination caused outbreaks in several countries in early 2022. Moreover, again, ringing the warnings, the fine line among new variants, and the risk of resistance to already developed vaccines [9,10]. In particular, the omicron variant has many mutations in the Spike protein. These mutations may contribute to the low efficacy of current vaccines and provide virus evasion and already immunized people [11].

According to recent studies, COVID-19 vaccines approved to date produce serum IgG1 but leave nasal epithelium and upper respiratory tract unprotected. As a result, they allow the SARS-CoV-2 infection (i.e., not providing mucosal immunity) [12]. What makes necessary new pathways for COVID-19 infection therapies? In this instance, natural or synthetic compounds are an awesome font to discover new antiviral drugs. Plant compounds include an extensive list of biologically active molecules. Several of them have antiviral activity [13]. Thus, they are a good starting point for the search against those interactions with virus proteins.

The SARS-CoV-2 main protease (Mpro) is a promising drug target. This protein plays a crucial role in viral replication and transcription [14]. Mpro is conserved among coronaviruses, sharing ~76% sequence similarity with SARS-CoV-1 Mpro. In addition, there is no human host cell protease with similar substrate specificity [15].

At last, molecular docking is an excellent methodology for predicting their protein-ligand interaction. Several endpoints, such as interactive activity, interaction energy, and ligand-specific interaction region, are essential in that approach. Consequently, molecular docking studies could help model the ligand-receptor interaction to identify potential SARS-CoV-2 Mpro pharmacophore sites. Herein, it aims to test 35 natural compounds as potential inhibitors of the SARS-CoV-2 major protease. In addition, it analyzed the computational pharmacokinetic parameters and predicted their toxicological effects on humans. Lastly, this study resembles information on a drug structure through standard and drug similarity.

Methods

Molecular docking studies

Molecular docking was performed via the Chimera tool, using the AutodockVina tool to predict the protein-ligand interaction described elsewhere [16]. Docking process possessing parameter of maximum reiteration of 1500, maximum population size 50, Grid solution 0.2 having a binding affinity, the protein and ligands were evaluated on the following confirmation of the Internal Electrostatic interaction (Internal ES), sp2-sp2 torsions and internal hydrogen bond interaction. The binding site is defined as the first cavity possessing high volume. A post dock study involves energy minimization and H-bond optimization. Setting of Simplex Evolution at max steps 300 and neighbor distance faster 1.00 [16]. The method for docking calculation consists of using the MMFF94 parameter as a Geometry Optimization Method, where a force field aims to minimize the energy of the ligand. The solvation parameters are set by AutoDockVina concurrently with the docking simulations [17]. The docking validation was following the instructions presented elsewhere [18].

Ligands preparation

In this work, there are evaluated 35 phytochemical components from various plants using a molecular docking protocol. Some compounds have antiviral activities described yet: Myricitrin, Methyl rosemary, 5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glycopyranoside, calceolarioside B, Myricetin 3-O-beta-D-glucopyranoside, Licoleafol, Amarantine, Berberine, Caffeine, Capsaicin, Embelin, Emodin, Gossypol, Hypericin, Luteolin, Oxyacanthine, Sanguinarian, Crocin, Digitoxigenin, β-eudesmol, Kaempferol, Quercetin, Naringenin, Oleuropein, Catechin, Curcumin, Epicatechin-gallate, Zingerol, Gingerol, Allicin, Resveratrol, Pterostilbene, Pinosilvin, Piceatannol. The ligand structures were taken from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in mol2 format for docking analyses.

Protease preparation

Mpro three-dimensional (3D) structure was chosen for the *in silico* test against those natural compounds. This structure is available at the Protein Databank in a complex with an inhibitor (PDB ID: 6LU7). The 3D structure of the SARS-CoV-2 main protease was downloaded from Protein Data Bank (https://www.rcsb.org). The 6LU7 protein is a homodimer and contains 306 amino acid residues, and two chains, named A and B. Chain A was used for macromolecule preparation. As performed in Sahin, et al., the water molecules were removed, and nonpolar hydrogen molecules were added to the protein structure in the Python molecule viewer setting of mgltools, and a [17;19]. The complexed inhibitor was removed using UCSF Chimera 1.15, and the apoprotein was saved in PDB format [20]. The protein was minimized using SwissProt PDBviewer 4.1 as described elsewhere [21].

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ADME analysis

Using the canonical SMILES chemical nomenclature of each ligand under consideration, it performed Absorption, Distribution, Metabolism, and Excretion (ADME) prediction. Then, the molecules are uploaded in SMILES format to the SwissADME server (http://www.swissadme.ch). We subsequently surveyed HIV protease inhibitors, already authorized by the FDA as positive controls. Thus, with this approach, some parameters were established among the tested molecules and some inhibitors already on the market.

Results

Molecular docking studies

Molecular docking was performed for 35 phytochemical components against Mpro using UCSF Chimera 1.15 to identify molecular interactions between the protein active site and ligands. The binding energy (ΔG) in these complexes' best poses is shown and compared in Figure 1. The best ligands were those with the highest binding energy, including Myricitrin, Calceolarioside B, Hypericin, Epicatechin-gallate, (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside and Calceolarioside B.

The interaction analysis of these natural molecules with the virus protease revealed specific residues, including when interacting with the (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside (Trp207, Ser284, and Glu288), Hypericin (Glu166, Arg188, and Thr190), Calceolarioside B (Gly143, Ser144, Cys145, Glu166, Arg188, and Gln192), Epicatechin (Ser144, His163, and Leu167) and Myricitrin (Thr190) (Figure 2). These data may indicate that these compounds may be a feasible option to explore against some specific mutants of this coronavirus.

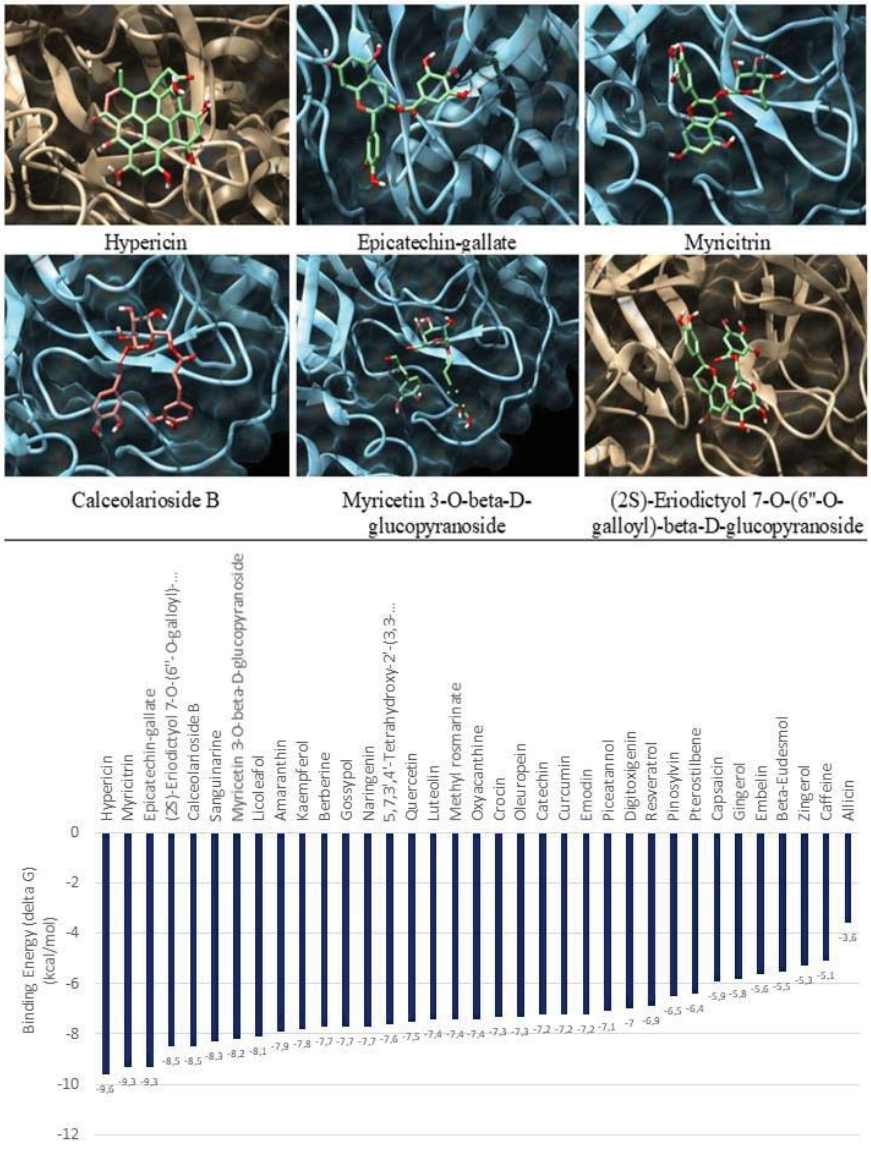

Figure 1: Interaction of COVID-19 main protease with the best pose of different molecular compounds from bark, leaves, and roots of various plants and Binding Energy (ΔG = kcal/mol).

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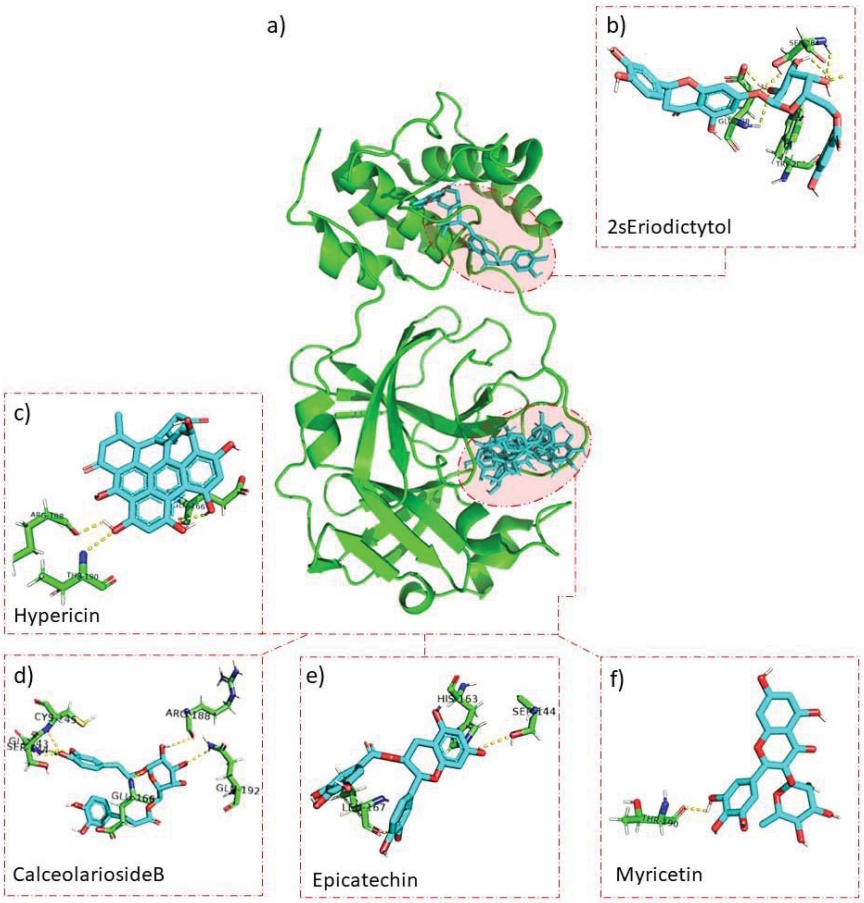

Figure 2: By molecular docking, it was possible to establish that the molecules interacted with specific residues of the protease, (a) 6LU7 with(b) (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside (Trp207, Ser284, and Glu288), (c) Hypericin (Glu166, Arg188, and Thr190), (d) Calceolarioside B (Gly143, Ser144, Cys145, Glu166, Arg188, and Gln192), (e) Epicatechin (Ser144, His163, and Leu167) and (f) Myricitrin (Thr190). The obtained ΔG value was -8.5, -9.6, -8.5, -9.3 and -9.3 kcal/mol, respectively.

ADMET prediction

The analysis of the physical and chemical properties of all molecules, their lipophilicity, and drug likeliness are shown in Table 1. The rule of five (RO5) predicts that good absorption is more likely when the molecular weight is lower than 500, the value of the topological polar surface area is in the range of 20-140 Å^2, and the value of Molecular Refractivity in the range 40-130 and there are less than 5 H-bond donors and 10 H-bond acceptors.

Discussion

Molecular docking is a fundamental tool for intermolecular interaction prediction. These results might direct subsequent studies. Herein, the lowest docking score determined the preferred best ligand as it indicates more excellent stability of the binding [22]. Based on molecular docking results among the phytochemicals with the Mpro active site, six compounds exhibited better binding efficacy against the target. Compared to the other phytochemicals, these compounds are Myricitrin, (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside, Calceolarioside B, Myricetin 3-O-beta-D-glucopyranoside, Hypericin, and Epicatechin-gallate.

In another inhibitor analysis, the peptide inhibitor N^3 and ∝-ketamine interacted via hydrogen bonds with residues in the protease binding site. The interactions happen among the compounds and Thr190, His163, Cys145, Glu166, and Gly143 protein residues. These residues are also the interaction targets of the ligands tested in our study Hypericin, Epicatechin, Myricitrin, and Calceolarioside B [23].

Another study shares these interaction residues. Interactions with Remdesivir (Cys145, Glu166, Gln192, and Thr190), GS441524 (Glu166, Gln192, and Thr190), Arbidol (His163, Glu166, and Leu167), Glycyrrhizin (Glu166, Cys145, and Ser144) and native co-crystal ligand (O6K) (Glu166 and His163) were found to interact with these regions of the protease [24] specifically. Mpro has three domains, consisting of residues 8-101 (Domain I), 102-184 (Domain II), and 201-303 (Domain III) [25]. This result indicates that the most relevant ligands in our research are between domains I and II of Mpro. Our data indicate a ΔG close to or higher than those found in other works that tested other natural producers, such as the generous *Aloe [26]*, Xylopic acid, Resveratrol, Ellagic acid, Kaempferol, and Quercetin [27] and diterpenoids and bioflavonoids of TorreyaNucifera leaves [28].

This rule describes molecular properties that are important for the pharmacokinetics of a drug in the human body. This

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Table 1: Physiochemical properties, lipophilicity, and drug-likeness of the natural compounds and FDA-approved protease inhibitor positive controls (Grey shadow).

Ligand	Formula	Molecular weight (g/mol)	Num. heavy atoms	Num. H-bond acceptors	Num. H-bond donors	Molar Refractivity	TPSA (Å²)	Consensus Log $P_{o/w}$	Bioavailability Score
Allicin	$C_6H_{10}OS_2$	162.27	9	1	0	45.88	61.58	1.61	0.55
Amaranthine	$C_{30}H_{34}N_2O_{19}$	726.59	51	19	11	167.15	345.60	-4.75	0.11
Berberine	$C_{20}H_{18}NO_4$	336.36	25	4	0	94.87	40.80	2.53	0.55
Beta-Eudesmol	$C_{15}H_{26}O$	222.7	16	1	1	70.46	20.23	3.61	0.55
Caffeine	$C_8H_{10}N_4O_2$	194.19	14	3	0	52.04	61.82	0.08	0.55
Calceolarioside B	$C_{23}H26O_{11}$	478.45	34	11	7	117.20	186.37	0.36	0.17
Capsaicin	$C_{18}H_{27}NO_3$	305.41	22	3	2	90.52	58.56	3.43	0.55
Catechin	$C_{15}H_{14}O_6$	290.27	21	6	5	74.33	110.38	0.85	0.55
Crocin	$C_{44}H_{64}O_{24}$	976.96	68	24	14	227.19	391.20	-2.75	0.17
Curcumin	$C_{21}H_{20}O_6$	368.38	27	6	2	102.80	93.06	3.03	0.55
Digitoxigenin	$C_{23}H_{34}O_4$	374.51	27	4	2	104.76	66.76	3.27	0.55
Embelin	$C_{17}H_{26}O_4$	294.39	21	4	2	84.31	74.60	3.68	0.56
Emodin	$C_{15}H_{10}O_5$	270.24	20	5	3	70.78	94.83	1.87	0.55
Epicatechin-gallate	$C_{22}H_{18}O_{10}$	442.37	32	10	7	110.04	177.14	1.23	0.55
(2S)-Eriodictyol 7-O-(6"-O-galloyl)-beta-D-glucopyranoside	$C_{28}H_{26}O_{15}$	602.50	43	15	9	141.42	253.13	0.09	0.17
Gingerol	$C_{17}H_{26}O_4$	294.39	21	4	2	84.55	66.76	3.13	0.55
Gossypol	$C_{30}H_{30}O_8$	518.55	38	8	6	148.90	155.52	5.04	0.17
Hypericin	$C_{30}H_{16}O_8$	504.44	38	8	6	144.83	155.52	4.26	0.17
Kaempferol	$C_{15}H_{10}O_6$	286.24	21	6	4	76.01	111.13	1.58	0.55
Licoleafol	$C_{20}H_{20}O_7$	372.37	27	7	5	98.48	127.45	2.01	0.55
Luteolin	$C_{15}H_{10}O_6$	286.24	21	6	4	76.01	111.13	1.73	0.55
Methylrosmarinate	$C_{19}H_{18}O_8$	374.34	27	8	4	95.72	133.52	2.00	0.55
Myricetin 3-O-beta-D-glucopyranoside	$C_{21}H_{20}O_{13}$	480.38	34	13	9	112.18	230.74	-0.96	0.17
Myricitrin	$C_{21}H_{20}O_{12}$	464.38	33	12	8	111.02	210.51	-0.23	0.17
Naringenin	$C_{15}H_{12}O_5$	272.25	20	5	3	71.57	86.99	1.84	0.55
Oleuropein	$C_{25}H_{32}O_{13}$	540.51	38	13	6	127.28	201.67	0.02	0.11
Oxyacanthine	$C_{37}H_{40}N_2O_6$	608.72	45	8	1	181.60	72.86	5.12	0.55
Piceatannol	$C_{14}H_{12}O_4$	244.24	18	4	4	69.90	80.92	2.14	0.55
Pinosylvin	$C_{14}H_{12}O_2$	212.24	16	2	2	65.86	40.46	2.90	0.55
Pterostilbene	$C_{16}H_{16}O_3$	256.30	19	3	1	76.82	38.69	3.31	0.55
Quercetin	$C_{15}H_{10}O_7$	302.24	22	7	5	78.03	131.36	1.23	0.55
Resveratrol	$C_{14}H_{12}O_3$	228.24	17	3	3	67.88	60.69	2.48	0.55
5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	$C_{20}H_{18}O_6$	354.35	26	6	4	99.73	111.13	3.07	0.55
Sanguinarine	$C_{20}H_{14}NO_4$	332.33	25	4	0	94.68	40.80	2.88	0.55
Gingerol	$C_{11}H_{16}O_3$	196.24	14	3	2	55.51	49.69	1.86	0.55
Amprenavir	$C_{25}H_{35}N_3O_6S$	505.63	35	7	3	133.62	139.57	2.50	0.55
Atazanavir	$C_{38}H_{52}N_6O_7$	704.86	51	9	5	193.76	171.22	3.82	0.17
Darunavir	$C_{27}H_{37}N_3O_7S$	547.66	38	8	3	142.20	148.80	2.45	0.55
Fosamprenavir	$C_{25}H_{36}N_3O_9PS$	585.61	39	10	4	144.53	195.91	1.70	0.11
Indinavir	$C_{36}H_{47}N_5O_4$	613.79	45	7	4	182.62	118.03	2.76	0.55
Lopinavir	$C_{37}H_{48}N_4O_5$	628.80	46	5	4	187.92	120.00	4.37	0.55
Nelfinavir	$C_{32}H_{45}N_3O_4S$	567.78	40	5	4	166.17	127.20	4.33	0.55
Ritonavir	$C_{37}H_{48}N_6O_5S_2$	720.94	50	7	4	197.82	202.26	5.04	0.17
Saquinavir	$C_{38}H_{50}N_6O_5$	670.84	49	7	5	192.87	166.75	3.17	0.17
Tipranavir	$C_{31}H_{33}F_3N_2O_5S$	602.66	42	9	2	153.80	113.97	6.06	0.56

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rule can be used when creating drugs. The active drug is gradually optimized to increase the activity and selectivity of the compound and to ensure that the physicochemical properties inherent in compounds obeying the Lipinski rule are maintained.

Bioavailability Score is based on a probability value of a molecule to have an optimum profile of permeability and bioavailability, where 0.55 indicates the obedience of the Lipinski rule of five. A molecule can be considered a good drug if all the computational filters of SwissADME - Lipinski, Ghose, Veber, Egan, and Mueggehave no violations.

Myricitrin, Calceolarioside B, and Myricetin 3-O-beta-D-glucopyranoside have several H-bond acceptors equal to 12, 11 and 13, respectively, which is more than ten acceptable. The molecular weight of (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside is not lower than 500 g/mol and equal to 602.50 g/mol as well as Hypericin. Epicatechin-gallate showed the value of topological polar surface area equal to 177.14 $Å^2$, which is not in the excellent range of 20-140 $Å^2$.

The lipophilicity study revealed that values of Log Po/w (Consensus Log Po/w) of Gossypol and Oxyacanthine are out of the acceptable five and equal to 5.04 and 5.12, respectively. In addition, Myricitrin, Myricetin 3-O-beta-D-glucopyranoside, Amaranthine, and Crocin have negative lipophilicity values, which is unfavorable.

Hypericin is an anthraquinone derivative naturally found in the yellow flower of *Hypericumperforatum* with an antidepressant, potential antiviral, antineoplastic and immunostimulating activities [29]. It has the highest docking score (-9.6 Kcal/mol) with the main coronavirus protease among all the phytochemicals.

The use of molecules available in nature offers an advantage for the bioavailability of these compounds. Considering the results obtained from molecular docking studies, the phytochemicals Myricitrin, (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside, Calceolarioside B, Myricetin 3-O-beta-D-glucopyranoside, Hypericin, and Epicatechin-gallate can be considered for exploring in COVID-19 treatment. These phytochemicals have shown comparable coronavirus main protease *in silico* inhibitory.

Flavonoid Myricitrin is found in vegetables, fruits, nuts, berries, herbs, plants, tea, wine, and medicinal plants. Myricitrin is nitric oxide (NO) and protein kinase C (PKC) inhibitor that has central nervous system activity, including anxiolytic-like action [30] docked with a target with a docking score of -9.3 Kcal/mol.

Myricetin 3-O-beta-D-glucopyranoside is a compound with chemotherapeutic, chemopreventive, and antiangiogenic properties [31], a naturally occurring plant metabolite found in several food items such as blackcurrant, typical grape, highbush blueberry, and tea docked with the target with a docking score of -9.3 Kcal/mol.

Epicatechin-gallate, a flavonoid present in brewed black, green, and oolong teas, cherries, and strawberries inhibit the growth of cancer cells, and gas anti-inflammatory effects show a docking score of -9.3 Kcal/mol [32].

(2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside isolated from the leaves of *Acer mono* possessing antioxidant activity [33], has binding efficacy with a target with a docking score of -8.5 Kcal/mol. Calceolarioside B, a natural product found in *Lepisoruscontortus [34]* binds with a docking score of -8.5 Kcal/mol.

Compounds conforming to Lipinski's rule are less intensively consumed during clinical trials and therefore have an increased likelihood of entering the market. In addition, according to Lipinski's rule, the molecular weight should be less than 500 g/mol. This characteristic is necessary to transport the ligand into cells easily. The octanol-water distribution coefficient (logP) characterizes the ability to transport drugs through cell membranes, determining their absorption and distribution in various body systems. A negative logP value means that the compound has a higher affinity to the aqueous phase; when logP = 0, the compound is equally distributed between the lipid and aqueous phases; a positive logP value means a higher concentration of the compound in the lipid phase [35-38].

Lipinsky's Rule of Five perspectives can conclude that none of the phytochemicals above has properties that make it an orally active drug. Thus, they may require different formulations, including nanotechnology or strategy/administration routes *(e.g.,* use of injection). However, compared with the FDA-approved protease inhibitor positive controls, they may still have a good profile that should be evaluated by *in vitro* and *in vivo* assays.

Based on these results, we can highlight that in a globalized world, where territorial barriers are easily broken by airplane and boat trips that daily take hundreds of individuals from countries with low vaccination coverage to other locations of the globe, igniting an alert for the importance of investments in pharmacological alternatives against SARS-Cov-2.

Conclusions

With molecular docking, the screening results in 35 natural products as possible competitive inhibitors of SARS-Cov-2 main protease. In addition, molecular docking studies disclosed the high binding affinities of (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside, Hipericina, Calceolarioside B, Epicatechin and Myricitrin.

Physicochemical parameters also showed promising properties of drug-likeness. The current study results conclude that the complexity of natural compounds can be considered a preventive measure to reduce or prevent the effects of COVID-19. Further research should be conducted to verify the potency and safety of these compounds in the treatment of COVID-19.

Declarations

Contributions: ES, VGOE, RBG, and HCC performed the research and manuscript writing. JSN assisted in the

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bibliographic organization and carried out the writing of the manuscript. ES, MVS, VGOE performed the computational experimental work, analyzed the data, created the figures and tables and wrote the manuscript. RBG, HCC, MK, and CRR were responsible for the final review of the research and approval of the final content of the manuscript. All authors read and approved the final manuscript

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