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REVIEW

Bioactive compounds as potential angiotensin-converting enzyme II inhibitors against COVID-19: a scoping review

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Abstract
Objective and design The current study aimed to summarize the evidence of compounds contained in plant species with the ability to block the angiotensin-converting enzyme 2 (ACE-II), through a scoping review.
Methods PubMed and Scopus electronic databases were used for the systematic search and a manual search was performed
Results Studies included were characterized as in silico. Among the 200 studies retrieved, 139 studies listed after the exclusion of duplicates and 74 were included for the full read. Among them, 32 studies were considered eligible for the qualitative synthesis. The most evaluated class of secondary metabolites was flavonoids with quercetin and curcumin as most actives substances and terpenes (isothymol, limonin, curcumenol, anabsinthin, and artemisinin). Other classes that were also evaluated were alkaloid, saponin, quinone, substances found in essential oils, and primary metabolites as the aminoacid L-tyrosine and the lipidic compound 2-monolinolenin.
Conclusion This review suggests the most active substance from each class of metabolites, which presented the strongest affinity to the ACE-II receptor, what contributes as a basis for choosing compounds and directing the further experimental and clinical investigation on the applications these compounds in biotechnological and health processes as in COVID-19 pandemic.

Keywords Coronavirus · ACE-II · Plants · Secondary metabolite · Treatment

Abbreviations

ACE-II	Angiotensin-converting enzyme II
AT1	Angiotensin I receptor
CLpro	Chymotrypsin-like protease
COVID-19	Coronavirus disease 2019
H1N1	Influenza A virus
HIV	Human immunodeficiency virus
IFN	Interferon

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MERS-CoV	Middle East respiratory syndrome coronavirus
MOE	Molecular operating environment
NLRP3	NLR family pyrin domain containing 3
OSF	Open science framework
PDB	Protein Data Bank
PRISMA-ScR	Systematic reviews and meta-analyses extension for scoping reviews
PRR	Pathogen recognition receptors
RAAS	Renin–angiotensin–aldosterone system
RBD	Receptor binding domain
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S	Spike protein
TMPRSS2	Human transmembrane protease
VMD	Visual molecular dynamics
WHO	World Health Organization

Introduction

Several efforts have been performed to manage the COVID-19 pandemic (coronavirus disease 2019), responsible for causing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including the recent vaccination programs rolled out worldwide. However, there is still a need to identify effective treatments, particularly in countries where not only the vaccine uptake is slow, but also the insidious threat of mutations has led to a vaccine escape and an increase of infections [1–3]. Up until 31th of January 2022, the global situation is that more than 373 million cases of COVID-19 were confirmed, with over 5 million deaths [4].

The angiotensin-converting enzyme 2 (ACE-II), a type I membrane protein found in the lung, arteries, heart, liver, and kidney cells, plays an important role in the renin–angiotensin–aldosterone system (RAAS), involving blood pressure regulation and electrolyte homeostasis. ACE-II cleaves angiotensin-II to angiotensin (1–7) which exerts vasodilating, anti-inflammatory, and antifibrotic effects through binding to the receptor. Additionally, by coordinating the bradykinin metabolism in the lungs, ACE-II can inhibit both vasodilation and elevation of vascular permeability [5–7].

ACE-II has an active enzyme domain exposed on the cells surface that acts as a functional receptor allowing, among others, the entry of the SARS-CoV-2 virus (i.e. etiological agent of the new coronavirus disease—COVID-19) into human cells, especially in the upper respiratory tract [7]. The viral Spike (S) protein of the SARS-CoV-2 has a high binding affinity to ACE-II, which leads to the S-protein priming by the host cell transmembrane protease serine 2 (TMPRSS2) and fusion of the virus with cell membranes to release the virus RNA genome into the host cell through receptor-mediated endocytosis [8–10].

According to the literature, nearly 80% of the world's population depends on traditional medicines to treat a range of diseases. The past experiences with the influenza outbreak, MERS-CoV, and HIV infections proven that natural products, such as medicinal plants and their derivatives, are valuable sources for the synthesis of new antiviral drugs due to their availability and variety of substances with therapeutic potential [11, 12]. Substances such as flavonoids (e.g. hesperidin, baicalin, rutin), xanthones, and alkaloids (e.g. ergotamine, nigellidine, quinadoline B) have antiviral, antibacterial and anti-inflammatory activities [13, 14]. Additionally, there is evidence that plant species from traditional Indian system of medicine are capable of reducing infection caused by SARS-CoV-2 by modulating the anti-inflammatory effects on the organism and by inhibiting the replication and modulation of fluids in the viral membrane. Some substances can also inhibit proteins that are paramount for the infection's process such as the ACE-II, TMPRSS2 or NLRP3 (i.e. molecular platform that promotes inflammation) in the host [15].

Although the role of the ACE-II receptor in the pathophysiology of COVID-19 is not yet fully elucidated. It is known that drugs that act on this enzyme may prevent the entry of the virus into the cell and also increase its expression in the tissue, suggesting a protective effect on the pulmonary inflammatory process. In addition, the search for substances with therapeutic potential for COVID-19 is moving towards drugs with multiple therapeutic targets, acting on key sites of the disease, such as ACE-II receptors [16, 17].

In this context, the aim of this scoping review was to synthesize the available evidence on the effects of metabolites from plants with potential to inhibit ACE-II receptor, thus preventing the entry of SARS-CoV-2 in the respiratory tract.

Methods

Research question

This scoping review was performed according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [18], Cochrane Handbook for Systematic Reviews of Interventions [19], and the Joana Briggs Institute [20]. The study was registered in Open Science Framework (OSF) and its protocol is available at https://doi.org/10.17605/OSF.IO/7QXV8.

Search strategy

The search was conducted in the electronic databases PubMed and Scopus with no restriction for publication date (October the 5th, 2020). Manual searches were performed in the references from the included articles. The main descriptors used were: "ACE-II", coronavirus, COVID-19 and "herbal medicine" (see full strategy search in appendix A provided in the supplementary material).

Inclusion and exclusion criteria

We included in silico studies that evaluated the effect of bioactive compounds from plant species as potential treatment of infection caused by the SARS-CoV-2 virus (COVID-19) using ACE-II as the receptor. Other study designs, articles not assessing bioactive compounds or targeting different proteins and those published in non-Roman characters were excluded from this scoping review.

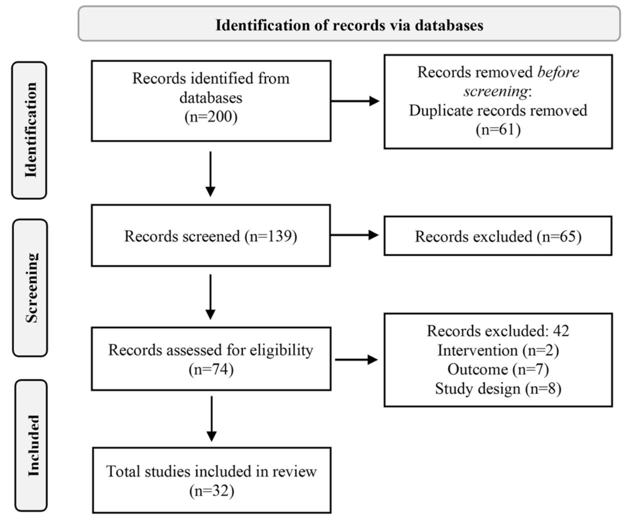

Fig. 1 Flow diagram of included records of the scoping review

Eligibility and data extraction

Relevant studies selected during screening (title and abstract reading) and eligible according to the above-mentioned criteria after full-text reading, had their data extracted using structured tables (general characteristics of the studies, metabolites classes, biding energy, software used and main findings). The Protein Data Bank (PDB) was consulted for the codes of target proteins. According to the nature of the data, qualitative data analyses and synthesis were performed.

The steps title and abstract reading (i.e. screening), full-text reading (i.e. eligibility) and data extraction were conducted by two reviewers independently, in case of disagreement, a third reviewer was consulted.

Results

A total of 200 registers were selected from the database after duplicates removal, of which 139 were included during screening (title and abstract reading) and 74 were included for full-text appraisal (see the complete list in appendix B provided in supplementary material). Finally, 32 registers studies meeting the eligibility criteria had their data extracted and analyzed [21–52]. No articles were identified through manual searches (Fig. 1).

The main characteristics of the included studies, grouped according to metabolites' classes, is depicted in Table 1. Studies were mostly performed in India ($n = 11$; 34.37%) and China ($n = 10$; 31.25%). Flavonoids ($n = 10$; 31.25%) and others phenolic compounds ($n = 5$; 15.62%), terpenes ($n = 5$; 15.62%), alkaloids ($n = 3$; 9.37%), saponins ($n = 3$; 9.37%), quinone ($n = 1$; 3.12%), substances found in essential oils ($n = 3$; 9.37%) were the bioactive compounds evaluated as representatives from secondary metabolism. As primary metabolites were founded aminoacid ($n = 1$; 3.12%) and lipidic compound ($n = 1$; 3.12%). Overall, crystallographic structures available at the Protein Data Bank (PDB) were used by 27 studies (84.37%). The main used programs were Autodock Vina, Cytoscape, Visual Molecular Dynamics (VMD), and Molecular Operating Environment v.2.2 (MOE). The table with chemical structure classification of substances mentioned in Table 1 is in appendix C provided in the supplementary material.

Phenolic compounds

From the eligible studies, 15 (46.87%) evaluated the bonds in phenolic compounds. Among them, five used the PDB 1R42 (native human angiotensin-converting enzyme-related carboxypeptidase) and three, the PDB 2AJF (structure of SARS coronavirus spike receptor-binding domain complexed with its receptor). The other PDBs were used by only one study each, like 4APH (human angiotensin-converting enzyme in complex with angiotensin-II), 6VW1 (structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE-II) and 6M17 (2019-nCoV RBD/ACE2-B0AT1 complex). Three of these studies (20.0%) found quercetin as the best binder [31, 34, 40]. However, one study had observed a stronger binding capability from the substance curcumin in relation to the target ACE-II (PDB 1R42) [27], suggesting that the flavonoids, especially quercetin and curcumin are promising substances for the treatment of COVID-19 by multiple pathways.

Table 1 Main characteristics of the included records for ACE-II inhibition

Study (author, year)	Country	Metabolic group	PDB codes used	Main results	Programs
Secondary metabolites					
Huang et al., 2020	China	Betaxanthine	Uninformed	The indicaxanthin is the best ligand among the selected ligands (Probability value = 0.112)	Swiss Target Prediction (http://www.swisstargetprediction.ch/, version 2019); R 3.5.2; Cytoscape (https://cytoscape.org/, version 3.7.0); STRING (https://string-db.org/, version:11.0); cytoHubba (https://apps.cytoscape.org/apps/cytohubba, version 0.1); Entrez Gene
Joshi et al., 2020a	India	Estilbene derivative	2AJF	The δ-viniferine is the best ligand among the selected ligands (− 8.4 kcal/mol)	AutoDock Vina; Biovia Discovery Studio 4.5; PyMOL
Wahedi et al., 2020	Pakistan	Estilbene derivative	6VW1	The resveratrol is the best ligand among the selected ligands (− 8.0 kcal/mol)	Autodock/vina; Visual Molecular Dynamics (VMD); LigPlotþ; padrão de ligação Chimera e UCSF Chimera 1.14.; Chem office 2004; AMBER18; CPPTRAJ module; VMD 1.9.3
Balmeh et al., 2020	Iran	Flavonoid	Uninformed	The hesperidin is the best ligand among the selected ligands (− 7 kcal/mol)	AutoDock vina; Chimera software version 1.14; R software, version 4.0.0; Biorender software; Cytoscape 3.8.0
Liu et al., 2020	China	Flavonoid	1R42	The luteolin is the best ligand among the selected ligands (− 33.47 kJ/mol)	GraphPad Prism 6; Cytoscape Version 3.7.0 and plug-in Network Analysis; computing simulation platform Discovery Studio (DS); PyRx; Uedit 32; DAVID v6.8 (https://david.ncifcrf.gov/); Cytoscape 3.7.0; TCMSP database
Maiti; Banerjee, 2020	India	Flavonoid	4APH	The theaflavin monogallate (TFMG) is the best ligand among the selected ligands (ki value = 11.9 µmol)	PyMol molecular visualization; PatchDock web server; AutoDock 4.0
Maroli et al., 2020	India	Flavonoid	Uninformed	The procyanidin A is the best ligand among the selected ligands (− 8.9 kcal/mol)	Autodock VINA; SAMSON software package; Gaussian 09, UCSF Chimera e Ligplot; GROMACS 2020.1 software package; visualization tool Gephi 0.9.2
Omotuyi et al., 2020	Nigeria	Flavonoid	6M17	The tectochrysin is the best ligand among the selected ligands (− 8.7 kcal/mol)	Platform (https:// mcule.com/); visual molecular dynamics [VMD]; GraphPad Prism; PyMOL; ChEMBL
Pandey et al., 2020	India	Flavonoid	Uninformed	The quercetin is the best ligand among the selected ligands (22.17 ± 3.04 kcal/mol)	PyMol; AutoDock tools; AutoDock Vina produced 9; GROMACS-2018.1; CgenFF;Sanjeevini: online software tools
Ren et al., 2020a	China	Flavonoid	2AJF	The isorhamnetin is the best ligand among the selected ligands (Consensus scoring = 6)	String Datasets (https://string-db.org/); Cytoscape (Version 3.5.0, available at http://www.cytoscape.org/); Ligandfit docking; DAVID
Ren et al., 2020b	China	Flavonoid	1R42	The quercetin is the best ligand among the selected ligands (− 32.64 kcal/mol)	PyRx software; AutoDock Vina software; Cytoscape 3.7.2 (http://www.cytoscape.org/); (DAVID) (http://david.ncifcrf.gov/home.jsp); Genomes (KEGG)

Table 1 (continued)

Study (author, year)	Country	Metabolic group	PDB codes used	Main results	Programs
Tao et al., 2020	China	Flavonoid	1R42	The quercetin is the best ligand among the selected ligands (−8.4 kcal/mol)	Cytoscape 3.7.2; STRING (https://string-db.org/cgi/input.pl); AutoDock Tools 1.5.6 software; AutoDock Vina 1.1.2; Pymol 2.3; Webgestalt;
Zong et al., 2020	China	Flavonoid	1R42	The puerarin is the best ligand among the selected ligands (−33.47 kcal/mol)	PyMOL software; AutoDock software; Vina; Cytoscape 3.6.1 software, feramenta online Omishare Tools; Chem Office; Omishare Tools (http://www.omicshare.com/tools/index.php/); DAVID database; Cytoscape software
Maurya et al., 2020	India	Phenolic acid	1R42	The curcumin is the best ligand among the selected ligands (−142.647 kcal/mol Mol dock score and −139.525 kcal/mol Interaction energy)	Molegro Virtual Docker (MVD-3.0.0); swissADME server; admetSAR server
Yu et al., 2020	China	Lignan Phenolic acid	2AJF	The phillyrin and chlorogenic acid are the best ligands among the selected ligands (Binding energy = −0.29 and −0.87 kcal/mol, respectively)	Metascape (http://metascape.org); Swiss-Model (https://swissmodel.expasy.org/); ZDOCK Server (http://zdock.umassmed.edu/); AutoDock 4.2.6; Autodock molecular docking software (version 2.5); pyMOL; TCMSP database (http://tcmspw.com/)
Abdelli et al., 2020	Argelia	Terpenoid	6VW1	The isothymol is the best ligand among the selected ligands (−5.7853 kcal/mol)	Molecular Operating Environment (MOE) software package; Hyperchem 8.0.8 software; iMODS; PASS-Way2Drug server; RS-WebPredictor 1.0 and swiss target prediction
Alazmi; Motwalli, 2020	Saudi Arabia	Terpenoid	6M1D	The limonin is the best ligand in the open conformation of ACE-II (11.0 kcal/mol)	YASARA energy minimization server; Autodock 4.2; Avogadro; Discovery studio visualizer; Phyre2 webserver; MGLTools; Verify3D; UCSF Chimera; Antechamber module of Amber-Tools18; Gromacs 2019; ProTox-II
Dave et al., 2020	India	Terpenoid	2AJF	The curcumenol is the best ligand (−5.88 kcal/mol)	Argus Lab 4.0.1; Biovia Discovery studio
			6VW1	The curcumenol is the best ligand (−6.31 kcal/mol)	
Joshi et al., 2020b	India	Terpenoid	1R4L	The anabsinthin is the best ligand among the selected ligands (−12.5 kcal/mol)	PharmaGist web servers; PyMOL software; MG Tools of AutoDock Vina software; Lig-plot + v'.1.4.5 software; DruLiTo too; admetSAR server
Sehailia; Chemat, 2020	Argelia	Terpenoid	6LZG	The artemisinin is the best ligand among the selected ligands (−6.6 kcal/mol)	AutoDock Vina software; UCSF Chimera1.1; PDBQT file; AutoDock Vina software; visual molecular dynamics (VMD) software; GROningen MAchine for Chemical Simulations (GROMACS)

Table 1 (continued)

Study (author, year)	Country	Metabolic group	PDB codes used	Main results	Programs
Gao et al., 2020	China	Alkaloid	1R42	The bicuculline is the best ligand among the selected ligands (−41.42 kJ/mol)	AutoDockTools1.5.6 Software; AutoDock Vina Software (http://vina.scripps.edu/); tools R 3.6.2, protein molecules; visualization software PyMOL; Cytoscape v3.8.1; DAVID 6.8; biological information analysis tools Cytoscape v3.8.1; Swiss Target Prediction (http://www.swisstargetprediction.ch/); STRING Online Database (https://string-db.org/)
Gutierrez-Villagomez et al., 2020	Mexico	Alkaloid	1R4L	The pipercyclobutanamide B is the best ligand among the selected ligands (−7.34 kcal/mol)	Protein Preparation Wizard and the Virtual Screening Workflow tools; Grid-Based Ligand Docking with; Maestro Schrödinger software; Visual Molecular Dynamics; Qik-Prop44 module of Maestro Schrödinger
Shah et al., 2020	India	Alkaloids	6LZG	The norreticulin is the best ligand among the selected ligands (Docking Score = −99.0)	protein data bank (https://www.rcsb.org/), ChemBioDraw Ultra 14.0; ChemBiodraw3D 14.0; Molinspiration Cheminformatics server (http://www.molinspiration.com); ProTox-II online too; Swiss ADME online tool
Mu et al., 2020	China	Saponin	1R42	The diosgenin is the best ligand among the selected ligands (−9.2 kcal/mol)	Open Babel 2.3.2 software; PYMOL 2.3.4 software; Autodock 4.2.6 software; AutoDock Vina 1.1.2; Cytoscape 3.7.2; KOBAS3.0; DAVID database; STRING database; Cytoscape 3.7.2
Poochi et al., 2020	India	Saponin	6M0J	The ursodeoxycholic acid is the best ligand among the selected ligands (Glide score = −7.739 kcal/mol and Glide energy = −48.990 kcal/mol)	Glide 5.5; OPLS3; Qikprop; PP-wizard; Glide XP model
Vardhan; Sahoo, 2020	India	Saponin	6M17	The glycyrrhizic acid is the best ligand among the selected ligands (−9.5 kcal/mol)	AutoDock Vina 1.1.2; Swiss-model online server; CABS-flex 2.0 online simulation tool; Gaussian 09 W; GaussView 5.0; online tool http://biosig.unimelb.edu.au/pkcsm/prediction; online tool molinspiration https://www.molinspiration.com/cgi-bin/properties
My et al., 2020	Vietnam	Essential oil	6LU7	The linalool is the best ligand among the selected ligands (−11.1 kcal/mol)	MOE 2015.10 program; UniProtKB; Worldwide; Quickprep tool
Silva et al., 2020	United States of America	Essential oil	6M0J, 6VX1, 6VW1, and 6M17	The (E,E)-α-farnesene is the best ligand among the selected ligands (DSnorm = −23.97 kcal/mol)	Molegro Virtual Docker v. 6.0.1 (Aarhus, Denmark);
Thuy et al., 2020	Vietnam	Essential oil	Uninformed	The diallyl tetrasulfide is the best ligand among the selected ligands (−14.06 kcal/mol)	MOE 2015.10 software; SYBYL-X 1.1 software; ChemBioOffice 2018 software; SYBYL-X 1.1 software

Table 1 (continued)

Study (author, year)	Country	Metabolic group	PDB codes used	Main results	Programs
Ahmad et al., 2020	Pakistan	Quinone	6VW1	The dithymoquinone is the best ligand between the interfaces SARS-CoV-2 and ACE-II (8.6 kcal/mol)	Autodock Vina; Auto Dock GUI program; Visual Molecular Dynamics (VMD); Chimera 1.14; AMBER 18 software; online SwissADME software; online ProTox-II software
Primary metabolites					
Han et al., 2020	China	Amino acid	3D0G	The L-tyrosine is the best ligand among the selected ligands (Score = − 6.5)	Autodock Vina v.1.1.2; PyMOL v.2.3 software; Molecular Operating Environment v.2.2 (MOE) software; Open babel v.2.4.1; ClusterONE; Cytoscape ClueGO; Cytoscape v.3.2.1 software; STRING; Swiss ADME database http://www.swissadme.ch/
Selvaraje et al., 2020	India	Lipidic compound	1R42	The 2-monolinolenin is the best ligand among the selected ligands (− 116.12 kcal/mol)	Autodock v4.2; Biovia Discovery Studio 4.5; CHARMM force field; Gromacs (g_mmpbsa) software; Gromacs 5.1.4; CHARMM force field

ACE-II angiotensin-converting enzyme

Terpenes

Terpenes were the second class of secondary metabolites with high number of published studies (n = 5) [21–23, 33, 36, 47]. The targets used were PDB 6VW1, 6M1D (ACE-II-B0AT1 complex), 1R4L (inhibitor bound human angiotensin-converting enzyme-related carboxypeptidase), 2AJF and 6LZG (structure of the new binding domain to the peak receptor of coronavirus complexed with its ACE-II receptor), were used in one study each. Substances that showed most promising results according to Table 1 were: isothymol [21], limonin [33], curcumenol [47], anabsinthin [23] and artemisinin [36].

Alkaloids

The antiviral potential of alkaloids were evaluated for three studies [38, 48, 49] with PDBs 1R42, 1R4L and 6LZG, described as targets substances with promising activities were bicuculline [48], pipercyclobutanamide B [49], and norreticuline [38].

Saponins

Three studies referred to the effects of the saponins diosgenin, ursodeoxycholic acid, and glycyrrhizic acid [28, 32, 42]. One PDB code was used in each study for determining the substance's binding energy with its target, which were, 1R42, 6M17, and 6M0J (crystal structure of peak receptor-binding domain SARS-CoV-2 bound to ACE-II). Among these, the most significant result was ursodeoxycholic acid, through molecular docking performed using the Glide 5.5 software, with a score of − 48.990 kcal/mol [32].

Others

Essential oils were studied in three articles, with substances obtained from species of *Allium sativum* L., *Melaleuca cajuputi* Powell, *Matricaria recutita* L., *Ocimum campechianum* Mill., and *Zingiber officinale* Roscoe. The compound that performed better when analyzed through molecular docking was (E,E)-α-farnesene, in an experiment carried out using the Molegro Virtual Docker v. 6.0.1, for this binding the molecule reached the score of − 23.97 kcal/mol [29, 39, 41]. The quinone (dithymoquinone) was evaluated in only one study [22].

Of all the articles analyzed, two investigated the binding of substances from the primary metabolism of plants with ACE-II, and the genera/species of the plants of the analyzed formulations were presented. The most promising results were associated with L-tyrosine (aminoacid) and 2-monolinolenin [37]. The PDBs used were the 3D0G (crystal structure of spike protein receptor-binding domain from the 2002–2003 SARS coronavirus human strain complexed with human-civet chimeric receptor ACE-II) and 1R42, respectively.

In general, considering the binding energies, the substances from each class with the strongest affinity with the ACE-II receptor were associated with PDBs code as shown in Fig. 2.

Discussion

In this scoping review, were evaluated the outcomes of in silico studies conducted with bioactive compounds from plants with potential to interact with the ACE-II receptor. This type of study was chosen for analysis because it allows computational searching of protein databases to find novel substances, which allows its application in the search for therapeutic options against the COVID-19 pandemic [22, 53].

SARS-CoV-2 binds to human ACE-II through the binding of the spike protein (S) that contains S1 and S2 subunits. The S1 subunit is the receptor's binding site that is responsible for binding with the host ACE-II, and the S2 subunit facilitates membrane fusion in host cells. The receptor's binding domain cleaves the ACE-II receptor so that SARS-CoV can enter host cells. Some studies have evaluated that plant metabolites have the ability to selectively bind and inhibit this receptor-binding domain. These ligands can potentially inhibit the Spike-RBD/TMPRSS2/ACE-II axis simultaneously in RBD and ACE-II [14, 43]. Thus, studies are needed to elucidate the details of this inhibition, which may be due to different mechanisms according to plant metabolites.

Plants are capable of producing, transforming and/or accumulating low molecular mass metabolites, classified as secondary or special metabolites, which provide advantages for the survival of the species and may present interesting biological and therapeutic activities [54]. Among them, phenolic compounds are one of the most representative classes, with antioxidant, antiinflammatory, antiviral, antiproliferative, antitumoral and hormonal activities described in the literature, among others. Depending on the number of phenolic rings, polyphenols can be classified into phenolic acids, flavonoids, stilbenes, lignans, and others [54–56].

A previous study comparing the efficacy of flavonoids from the *Sambucus nigra* L. species versus antivirals as oseltamivir and amantadine by means of real time mass spectrometry ionization, found that these bioactive compounds had antiviral activities against Influenza A virus (H1N1), by binding and consequently blocking the ability of the virus to infect host cells [57]. Similarly in vivo study demonstrated effects of flavonoids glycosides from *Houttuynia cordata* Thunb., as rutin, hyperin, isoquercitrin, and quercitrin, on influenza A virus (IAV)-induced acute lung injury (ALI) in mice. Some of the effects reported were: increased the survival rate and life span, lesser weight loss, lower lung index, intact lung microstructural morphology, milder inflammatory infiltration, lower levels of markers anti-inflammatory, and lung H1N1 virus titers. In addition, in vitro results associated of inhibited viral replication and signaling in cells with the flavonoids hyperin and quercitrin [58]. Further, in silico studies showed inhibitory activity of flavonoids against the 3CLpro protein of SARS-CoV-2, one the main pharmacological targets against COVID-19 [59].

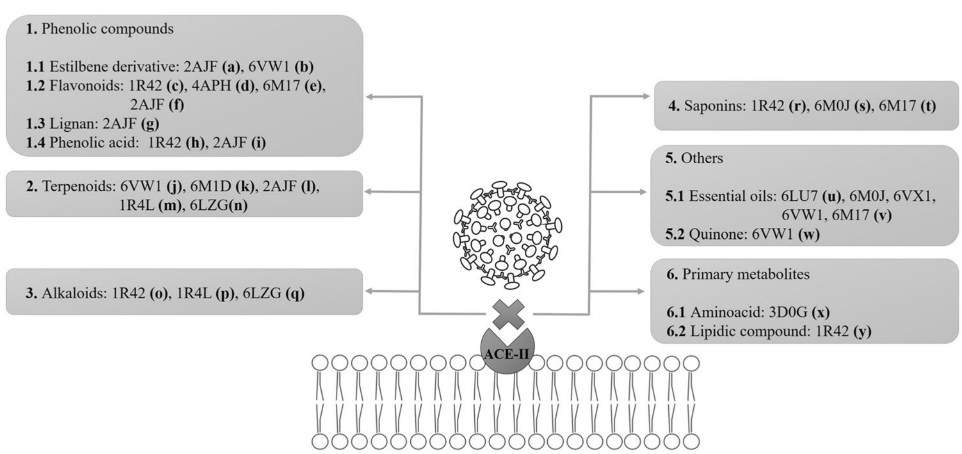

Fig. 2 Possible inhibition of SARS-CoV-2 binding to the ACE-II receptor by primary and secondary metabolites. **1.1.** (**a**) δ-viniferine; (**b**) resveratrol. **1.2.** (**c**) luteolin, quercetin, puerarin; (**d**) theaflavin; (**e**) tectochrysin; (**f**) isorhamnetin. **1.3.** (g) phillyrin. **1.4.** (h) curcumin, (**i**) chlorogenic acid. **2.** (**j**) isothymol, curcumenol; (**k**) limonin; (**l**) curcumenol; (**m**) anabsinthin; (**n**) artemisinin. **3.** (**o**) bicuculline; (**p**) pipercyclobutanamide B; (**q**) norreticulin. **4.** (**r**) diosgenin; (**s**) ursodeoxycholic acid; (**t**) glycyrrhizic acid. **5.1** (**u**) linalool, (**v**) (E,E)-α-farnesene; **5.2.** (**w**) dithymoquinone. **6.1.** (**x**) L-tyrosine; **6.2.** (**y**) 2-monolinolenin. Source: the authors

In this context, the studies included in this review show that the most studied class was flavonoids, as quercetin and curcumin with lower binding energies, which show potential of this class for development of new treatment strategies against COVID-19.

The antiviral activity has also been reported in studies that evaluated the biological activities of terpenes, which are classified according to the number of isoprene units in mono, di, tri, tetra, and sesquiterpenes. The andrographolide is a diterpene with known large anti-inflammatory activity and also has proved action against the viruses causing Influenza A, Hepatitis B, Hepatitis C, and Herpes Simplex. Among these substances, andrographolide is suggested to be a potential terpene for the treatment of SARS-CoV-2 due to its antiviral mechanism is the inhibition or reduction of binding protein's expression in these viruses [60]. More, artemisinin had promising results in docking analysis. This compound was found by Tu Youyou (Nobel Prize in 2015) in the *Artemisia annua* L. for the threat of malaria, known for its effects in the treatment of fever and chills, having a relatively safe toxicity profile [36]. Thus, its anti-inflammatory activity may be useful in alleviating respiratory distress syndrome associated with viral infections [61].

In a recent in vitro study, the hydroalcoholic extract of *Uncaria tomentosa* DC., majorly consisted by alkaloids (other class of secondary metabolites) was related to anti-inflammatory, immunomodulating, and antiviral activities, by inhibiting the release of infectious particles of SARS-CoV-2 and reducing the cytopathic effect caused by the virus in Vero E6 cellular lineage, thus being able to be considered a potential therapy against these viruses [62]. Other study demonstrated tetrandine, fangchinoline, and cepharanthine are potential antiviral agents for the prevention and treatment in the early stages infection of Coronavirus Human OC43 [63]. The alkaloids correspond to the group formed by diverse chemical compounds presenting at least a one basic nitrogen atom in any position of the molecule, as long as such nitrogen is not derived from an amide or peptide binding. This class of secondary metabolite has been used throughout the years due to its medicinal properties, including analgesic, cytotoxic, antifungal, antibacterial, and antiviral activity [64, 65]. Moreover, alkaloids showed antiviral and anti-inflammatory effects in acute respiratory distress syndrome against Influenza A infection, by interfering in signal transduction activated by PRR and IFN [66]. In addition, traditionally, these bioactive compounds are used in the treatment of some diseases as the use of lycorine for enterovirus, quinine for malaria, colchicine for gout arthritis, capsaicin/lidocaine for varicella-zoster virus, and vincristine and vinblastine for cancer, what highlights the possible applicability of alkaloids for treating COVID-19 [54, 67–70].

In this review, other classes of bioactive compounds evaluated were saponins and substances found in essential oils, which are also the focus of studies to assess the therapeutic potential, which have promising antiviral, antibacterial, antifungal, anti-inflammatory, and cytotoxic activities [23, 52, 71–73]. Regarding the reported primary metabolites, these are associated with the ability to modulate the anti-inflammatory response, as well antioxidant, antiviral, and antitumor activities [74]. The antiviral activity of the 2-monolinolein substance was a test for the African swine fever virus in an in vitro study, showed its capacity to inhibit the growth of the virus in a dose-dependent system [75]. For synthetized amino acids, antiviral activity for the hepatitis C virus was obtained when L-methionine and L-alanine were used [76]. An in vitro study carried out to evaluate the antiviral activity of polysaccharides in *Sargassum naozhouense* C.K. Tseng & Lu Baoren concluded that they have promising activity against herpes simplex virus [77].

According to the studies included in this review, the most promising classes of substances to act on the disease caused by the SARS-CoV-2 virus are flavonoids and terpenes. The main reasons are related to the fact that flavonoids (phenolic substances), such as quercetin and curcumin, have well-established antioxidant activity, and can act by reducing damage associated with oxidative stress, inflammatory disorders and reducing C-reactive protein, a marker in the process of COVID-19 infection. Terpenes, made up of isoprene units, can have multiple therapeutic actions, including antioxidant and antiviral actions, besides cardiovascular, rheumatological, neurological and inflammatory disorders [78, 79].

Thus, the evaluation of different substances with a specific purpose in pulmonary inflammation and action on ACE-II should be a point of reflection for the sectors involved, such as research and industry, requiring studies aimed at the characterization of new drugs with potential for treatment.

Our study has some limitations. No quantitative analyses were possible given the heterogeneity of data from different study designs and lack of common comparators. Results are only exploratory, however, because we followed a systematic and critical review process, individual bias from primary studies were reduced and the synthetized data may support the development of further studies in this field.

Conclusions

This scoping review synthetized the available evidence from in silico studies on the potential effects of bioactive compounds for treating COVID-19. The most evaluated class of secondary metabolites was flavonoids with quercetin and curcumin as most actives substances and terpenes with anabsinthin, isothymol, curcumenol, dithymoquinone, and limonin.

Thus, this review serves as a basis for choosing compounds and directing the further investigation in vitro, in vivo, and clinical trials on the applications these compounds in biotechnological and health processes as in COVID-19 pandemic.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest None declared.

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