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REVIEW ARTICLE

Flavonoid as possible therapeutic targets against COVID-19: a scoping review of *in silico* studies

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Abstract

Objectives This scoping review aims to present flavonoid compounds' promising effects and possible mechanisms of action on potential therapeutic targets in the SARS-CoV-2 infection process.

Methods A search of electronic databases such as PubMed and Scopus was carried out to evaluate the performance of substances from the flavonoid class at different stages of SARS-CoV-2 infection.

Results The search strategy yielded 382 articles after the exclusion of duplicates. During the screening process, 265 records were deemed as irrelevant. At the end of the full-text appraisal, 37 studies were considered eligible for data extraction and qualitative synthesis. All the studies used virtual molecular docking models to verify the affinity of compounds from the flavonoid class with crucial proteins in the replication cycle of the SARS-CoV-2 virus (Spike protein, PLpro, 3CLpro/MPro, RdRP, and inhibition of the host's ACE II receptor). The flavonoids with more targets and lowest binding energies were: orientin, quercetin, epigallocatechin, narcissoside, silymarin, neohesperidin, delphinidin-3,5-diglucoside, and delphinidin-3-sambubioside-5-glucoside.

Conclusion These studies allow us to provide a basis for in vitro and in vivo assays to assist in developing drugs for the treatment and prevention of COVID-19.

Keywords Coronavirus · Flavonoids · Respiratory Syndrome · *In silico*

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Introduction

The coronavirus 2019 disease (COVID-19), caused by the SARS-CoV-2 virus, has burdened global healthcare systems in an unprecedented way. Several scientific studies have been produced to reduce the impacts of this disease and side effects by developing new pharmacological treatments, vaccines, and faster and more sustainable diagnostic techniques. Among them, drug-repurposing studies have investigated the use of monoclonal antibodies (tocilizumab), antineoplastics (imatinib), immunosuppressants (mycophenolate mofetil), antiparasitics (niclosamide), and non-steroidal anti-inflammatory drugs steroids (glucocorticoids) [1].

Natural products are common models for synthesizing new antiviral drugs due to their availability in the nature and variability of compounds with therapeutic potential. Around 50% of all approved drugs between 1981–2019 were derivatives from natural products, including active ingredients,

such as flavonoids that can be found in several plant species, such as chamomile, mint, orange, lemon, apple, grape, among others [2].

Some flavonoids have important biological activities, such as antivirals (amentoflavone, baicalein, kaempferol, myricitrin, orientin, rutin), anti-inflammatory (hesperidin, phacelianin), antibacterial (naringenin), and immunomodulatory (fisetin, luteolin), and they can be used the prevention and treatment of different kind of diseases [3, 4]. The chemical structures of these natural metabolites are commonly composed of hydrophobic aromatic rings, hydroxyl groups, and sugar moieties (glucosides) that promote molecular interactions observed in silico studies [5].

Computer-Aided Drug Design (CADD) methodologies are used to study and develop new drugs or to reposition old drugs [6–8]. Molecular modeling is defined as the investigation of the structures and molecular properties of the substances of interest employing computational chemistry and graphic visualization techniques. Therefore, the researchers may obtain chemical or biological models, which are then submitted to specific computational programs to visualize, simulate, and interpret interrelated systems, such as those involved in drug-receptor interaction. These combined methods have the advantage of guiding a more assertive development of drugs and the possibility of reducing the wastage of time and investments in molecules with low therapeutic potential [9, 10].

Some recent studies highlight the potential antiviral effects of flavonoids against COVID-19. Santana et al. [11] showed that quercetin, apigenin, vitexin, baicalein, hesperidin, naringin, rutin, luteolin, and myricitrin were effective in reducing some of the main respiratory symptoms caused by COVID-19. An *in silico* approach using molecular docking to assess the inhibition of the SARS-CoV-2 spike protein revealed that naringin has minimal binding energy [12]. Similarly, Rameshkumar et al. [13] showed that agathisflavone and albireodelphin had high binding energies against RdRP and spike proteins, respectively. Five molecules were identified as potent inhibitors of the COVID-19 virus: albireodelphin, apigenin- 7-(6″-malonylglucoside), cyanidin-3-(*p*-coumaroyl)-rutinoside-5-glucoside, delphinidin-3,3-*O*-diglucoside-5-(6-*p*-coumarylglucoside) and (-)-maackiain-3-*O*-glucosyl-6″-*O*-malonate).

In the review study by Khazdair et al. [14], the flavonoid quercetin, when together with apigenin and isorhamnetin, inhibits the life cycle of the hepatitis C virus. In treating SARS-CoV-2, quercetin has been shown to act on the caspase 3, MAPK1, and NF-κB signaling pathways effectively to suppress high levels of cytokines and block binding sites on the surface peaks of SARS-CoV2 and prevent the spread of the virus.

Continuing the study of Khazdair et al. [14], an *in silico* research, it acts as a potentially highly effective disruptor of the initial infection process by binding to the interface between the SARS-CoV-2 viral spike protein and the ACE2 protein of epithelial cells.

Few other studies on this topic are available, like the study of Kaul et al. [15]. Our study aims to systematically synthesize the available data on the therapeutic potential of this class of natural substances for the treatment of SARS-CoV-2 infection, as well as their mechanisms of action, through a broad scoping review.

Methods

This scoping review was designed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist [16], Cochrane Handbook for Systematic Reviews of Interventions version 6.2, and Joanna Briggs Institute methodology for scoping reviews [17, 18]. This study was registered in the OSF (Open Science Framework), which can be found via the https://doi.org/10.17605/OSF.IO/7QXV8.

The search was performed in PubMed and Scopus electronic databases, on August 27th, 2020, without language or publication date limits. The main descriptors were related to COVID-19 and flavonoids (see the complete search strategy in appendix A provided in the supplemental material). Manual searches on the reference list of included studies were also conducted.

We included in silico studies that evaluated the use of flavonoids (any type and in any dose/regimen), alone or combined with other substances, for the management of SARS-CoV-2 (COVID-19) infections at any stage. During the screening phase (title and abstract) and full-text eligibility phase, articles were excluded if they were: (i) written in non-Roman characters; (ii) designed as case report; (iii) simple reviews; (iv) non-systematic; (v) systematic reviews with meta-analysis; (vi) systematic reviews without meta-analysis; (vii) about analyses of synthetic or; (viii) semi-synthetic flavonoids (see list of inclusion and exclusion criteria for studies in appendix B provided in the supplemental material).

A standardized form was used to extract the following data: study baseline characteristics (author, publication date), interventions/targets, PDB code, computer programs, and main effects/outcomes. These data were extracted from each article and synthetically transformed into the table presented in this study.

Two authors performed all steps in the study selection and data extraction phases independently, with a third author resolving discrepancies during the consensus meetings.

Results

The search strategy yielded 382 articles after the exclusion of duplicates. During the screening process, 265 records were deemed as irrelevant. From the 117 studies read in total, 80 were excluded, and 37 studies were included for qualitative synthesis (see Studies excluded after full reading in appendix C provided in the supplemental material). No additional article was added from the manual search (Fig. 1).

Table 1 below shows the main characteristics of these 37 studies included. All of these studies were designed as in silico essays, in which virtual molecular docking models were used to identify SARS-CoV-2 binding potential compounds, such as flavonoids.

The studies were published in 2020 and 2021, in the following countries: Australia (n = 1), Bangladesh (n = 1), China (n = 4), Egypt (n = 2), Germany (n = 1), India (n = 14), Iran (n = 1), Nigeria (n = 1), Pakistan (n = 1), Republic of Korea (n = 2), Saudi Arabia (n = 2), Spain (n = 1), South Africa (n = 1), Switzerland (n = 1), Taiwan (n = 1), United Kingdom (n = 1), and United States of America (n = 2).

The Schrodinger package, Amber18 software package, I-Tasser, Gromacs, PyRx, AutoDock, PharmaGist web server, Maestro package, MOE pharmacophore editor, Molegro Virtual Docker software, Ligplot software, Gold software, server SwissDock, Pymol, Discovery Studio software, Procheck web server, PerkinElmer, BiocManager Package, PatchDock web server, Austin Model-1, Open Babel software, UCSF Chimera, and Raccoon software were used as the main computer programs.

The main viral proteins analyzed were Glycoprotein S (Spike Protein) (n = 7 studies; 18.91%), Papain-type viral protease (PLpro) (n = 5 studies; 13.51%), Chymotrypsin-type viral protease (3CLpro) (n = 12; studies; 32.43%), Main protein (MPro) (n = 11; 29.73%), RNA-dependent RNA-polymerase (RdRP) (n = 6; 16.22%), and inhibition of the host's ACE II receptor (n = 11; 29.73%). (Complete information on the main flavonoid chemical structure is available in Appendix D of the supplementary material).

Studies of the Spike protein evaluated a total of 26 different flavonoids: apigenin, biochanin A, calophyllolide, kaempferol, cyanidin, daidzein, delphinidin, diosmetin, eriodictyol, fisetin, genistein, hesperidin, liquiritin, luteolin, tangeritin, malvidin, myricetin, morin, naringenin, orientin, pelargonidin, peonidin, phloridzin, quercetin, silymarin/ silibinin (silybin A), vitexin. With the most promising anti-viral compounds being: biochanin A (-78.41 kcal/mol); calophyllolide and eriodictyol (-7.90 kcal/mol); fisetin (-8.50 kcal/mol); hesperidin (-7.4 kcal/mol); quercetin (-86.22 kcal/mol); luteolin (-7.00 kcal/mol); orientin (-72.30 kcal/mol) [19–25].

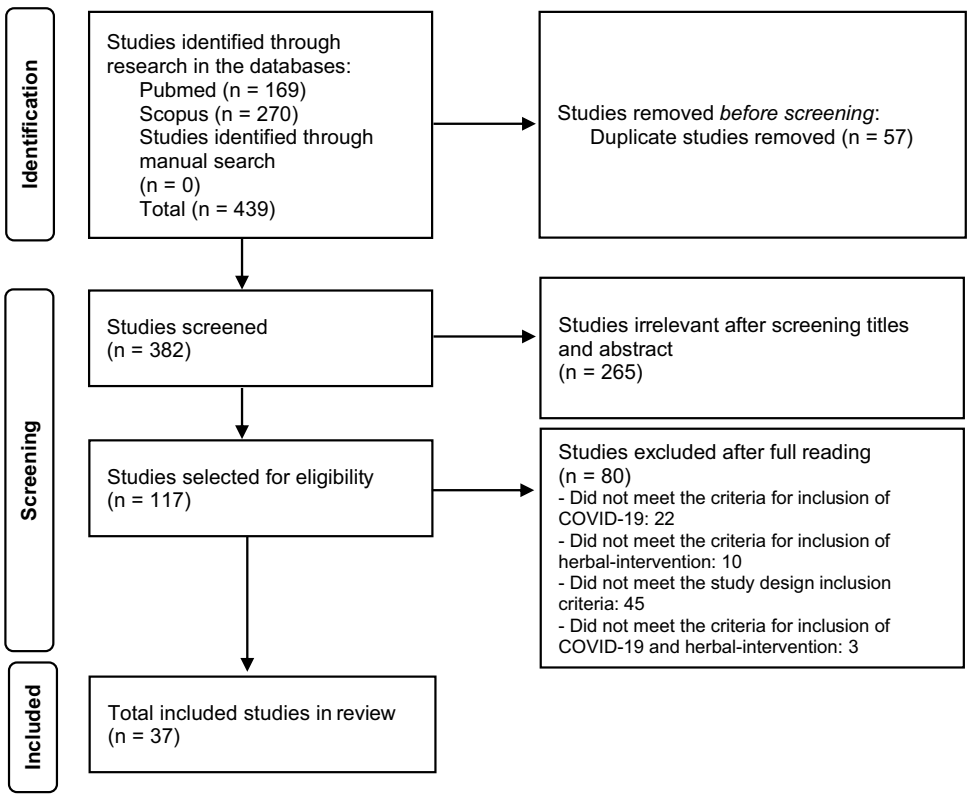


Fig. 1 Flowchart of the study selection process

Table 1 Main characteristics and results of the 37 in silico studies

Author and Year	Country	Flavonoids evaluated	Programs	Target protein and PDB code	Main results
Chikhale et al. 2020 [91]	United Kingdom	Neohesperidin, myricitrin, quercitrin, naringin, icariin	UniProtKB, Swiss-Model, Schrodinger Package	TMPRSS2 (serine transmembrane protease 2) (1Z8G)	Neohesperidin obtained the best bonding energy (-66.53 kcal/mol for Prime MM-GBSA), (-12,77 kcal/mol for Glide Score and Dock Score)
Bhowmik et al. 2020 [92]	India	Rutin	I-TASSER, PyRx, AutoDock, Genbank, Gromacs	Envelope (2MM4), membrane (4f91B) and nucleocapsid (6M3M)	Rutin showed better binding energy for envelope protein (-9.30 kcal/mol)
Hamza et al. 2021 [93]	Pakistan	Kaempferol	Mascot Server, Pymol, and BIOVIA Discovery Studio	Viral peptides	Kaempferol showed the best binding energy for viral peptides (-6.20 kcal/mol)
Fakhar et al. 2021 [94]	South Africa	Delphinidin-3-sambubioside-5-glucoside, delphinidin 3,30-di-glucoside-5-(6-*p*-coumarylglucoside), pelargonidin	Package Maestro, Pubchem, AMBER, QikProp Module	Mpro (6LU7)	Delphinidin-3-sambubioside-5-glucoside had the best binding energy (-12.37 kcal/mol)
Chitranshi et al. 2020 [29]	Australia	Apigenin, luteolin, quercetin, amentoflavone, bilobetin, ginkgetin	Clustal Omega Server, Interactive Tree of Life (iTOL) online tool, Austin Model-1, Open Babel software, Chimera software, AutoDock, Pubchem	3CLpro (6Y2G)	Amentoflavone showed the best binding energy (-8.49 kcal/mol)
Joshi et al. 2021 [35]	India	Cyanidin, kaempferol, rutin, gallocatechin, epigallocatechin, quercetin, eriodictyol	MEGA software, FigTree software, Cytoscape, AutoDock, AutoGrid, Pubchem, UniProtKB database, SwissADME Server	Mpro (6Y2F), RNA-dependent RNA polymerase (RdRP) (7BTF), ACE II (2AJF)	Quercetin and eriodictyol presented the best binding energy for Mpro (-9.90 kcal/mol) Epigallocatechin for RdRP (-12.90 kcal/mol) Cyanidin for ACE II (-8.20 kcal/mol)
Mahdian et al. 2020 [19]	Iran	Hesperidin	SWISS-MODEL, Drug Bank database, AutoDock, Gromacs package, PyRx tool	3CLpro, Plpro, TMPRSS2 (serine transmembrane protease 2), spike protein	Hesperidin presented the best binding energy for 3CLpro (-8.00 kcal/mol); for PLpro (-9.40 kcal/mol); for TMPRSS2 (-6.10 kcal/mol) and for protein spike (-7,40 kcal/mol)
Meyer-Almes 2020 [33]	Germany	Naringin, epicatechin, Homoorientin, proanthocyanidin, rutin, and quercetin	EOM pharmacophore editor, AutoDock, PyRx, Virtual screening using MOE ZINC15 database, AMBER	3CLpro (6LU7)	Naringin presented the best bonding energy (-9.70 kcal/mol)
Maiti and Banerjee 2020 [38]	India	Catechin, Catechin gallate, Epicatechin 3–*O*-gallate, epigallocatechin, epigallocatechin 3-gallate, gallocatechin, gallocatechin gallate, theaflavin monogallate, and theaflavin digallate	PatchDock web server, AutoDock, RCSB—PDB	ACE II (4APH)	Theaflavin monogallate presented the best binding energy for ACE II (- 6.72 kcal/mol)

Table 1 (continued)

Author and Year	Country	Flavonoids evaluated	Programs	Target protein and PDB code	Main results
Wang et al. 2020 [42]	China	Quercetin, formononetin, luteolin	BiocManager, Sybyl package, Software Cytoscape	Not applicable (Interleukins)	Quercetin showed the C-score above 3 for all tested targets
Vijayakumar et al. 2020 [22]	India	Luteolin, apigenin, tangeritin, kaempferol, quercetin, myricetin, fisetin, hesperidin, naringenin, eriodictyol, liquiritin, genistein, daidzein, calophyllolide, cyanidin, delphinidin, malvidin, pelargonidin, peonidin, phloridzin	SWISS-MODEL, PROCHECK, AutoDock, PerkinElmer Chem3D, PyRx, the Molinspiration, pkCSM and RCSB	RNA-dependent RNA polymerase (RdRP) (6M71), main protease (M pro) (6YB7) and Spike protein (S) (6LZG)	Calophyllolide showed the best binding energy for RdRP (-8.70 kcal/mol) and for Mpro (-9,30 kcal/mol Eriodictyol and calophyllolide showed the best binding energy for protein spike (-7.90 kcal/mol)
Jo et al. 2020 [5]	Republic of Korea	Baicalin, herbacetin, pectolinarin	Protein Preparation Wizard, Schrodinger Package (Maestro)	3CLpro (6LU7)	Pectolinarin presented the best bonding energy (-10.97 kcal/mol)
Khalifa et al. 2020 [32]	Egypt	Phacelianin, gentiodelphin, cyanidin 3-glucoside, cyanidin 3-rutinoside, pelargonidin 3-glucoside, delphinidin 3-sambudiglucoside	MOE (Molecular Operating Environment Software), PubChem, RCSB, GROMOS Software	3CLpro (6y84)	Cyanidin 3-rutinoside presented the best bonding energy (-17.02 kcal/mol)
Abian et al. 2020 [95]	Spain	Quercetin	AutoDock	3CLpro (6Y2E)	Quercetin showed the best binding energy (-7.50 kcal/mol)
Singh et al. 2020 [102]	India	EGCG (epigallocatechin-3-gallate), theaflavin (TF1), theaflavin-3'-*O*-gallate (TF2a), theaflavin-3'-gallate (TF2b), theaflavin-3,3'-digallate (TF3), hesperidin, quercetagetin, and myricitrin	AutoDock, Swiss Target Prediction, PubChem, RCSB, AMBER, PkCSM Tool	RNA-dependent RNA polymerase (RdRP) (6M71)	Theaflavin-3,3'-digallate showed the best binding energy (-9.90 kcal/mol)
Pandey et al. 2020 [21]	United States	Apigenin, luteolin, quercetin, kaempferol, fisetin, genistein	AutoDock, MGL Tools, PyMol, PubChem, RCSB	ACE II (6VYB), spike protein	Fisetin and quercetin showed identical and better binding energy for spike protein (-8.50 kcal/mol) Quercetin showed the best binding energy ACE II (-22.17 kcal/mol)
Sharma and Shanavas 2020 [39]	India	Delphinidin-3,5-diglucoside, avicularin	Package Schrödinger, RCSB – PDB, Swiss ADME software	Mpro (6lu7), ACE II (1R4L)	Delphinidin-3,5-diglucoside showed the best binding energy for Mpro (-12.20 kcal/mol); ACE II (-13.60 kcal/mol)
Fatoki et al. 2021 [26]	Nigeria	Quercetin, kaempferol	PyMol, AutoDock, Intact, Uniprot, DynaMine Server, Expression2Kinases Software, SwissADME	3CLpro (2XYR), PLpro (3VB6), RNA-dependent RNA polymerase (5Y3E)	Quercetin showed the best binding energy for 3Clpro (-8.20 kcal/mol); for PLpro (-10.20 kcal/mol); for RdRP (-9.20 kcal/mol)

Table 1 (continued)

Author and Year	Country	Flavonoids evaluated	Programs	Target protein and PDB code	Main results
Maurya et al. 2020 [20]	India	Quercetin, luteolin, naringenin	Molegro Virtual Docker, Pubchem, swissADME, admetSAR	ACE II (6VXX), Protein S (spike) (1R42)	Quercetin showed the best binding energy for spike protein (-86.22 kcal/mol) and for ACE II (-92.05 kcal/mol)
Tao et al. 2020 [34]	China	Quercetin, kaempferol, isorhamnetin, baicalein, naringenin, and formononetin	Cytoscape, AutoDock, Pymol, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform	ACE II (6lu7), 3CLpro (1r42)	Baicalein presented the best binding energy for 3CLpro (-7.80 kcal/mol) Quercetin showed the best binding energy for ACE II (-8.40 kcal/mol)
Kandeel et al. 2021 [27]	Saudi Arabia	Quercetin	Maestro Package, AMBER	PLpro (6w9c)	Quercetin showed the best binding energy (-7.75 kcal/mol)
Alagu et al. 2021 [24]	India	Orientin, vitexin	Autodock, Gromacs simulation package	Protein spike (S) (5R82), ACE II (6VYB), Mpro (1R42)	Orientin presented the best binding energy for Mpro (-90.20 kcal/mol); for protein spike (-72.30 kcal/mol); ACE II (-70.60 kcal/mol)
Chikhale et al. 2020 [36]	India	Quercetin	Schrodinger Package, glide XP, PubChem, RCSB, AMBER	ACE II (6M0J)	Quercetin showed the best binding energy for ACE II (-4.41 kcal/mol)
Narkhede et al. 2020 [96]	India	Hesperetin	AutoDock, Pymol, Discovery Studio Visualizer, PubChem, RCSB, SwissADME	Mpro (6LU7)	Hesperetin showed the best binding energy (-7.90 kcal/mol)
Ruan et al. 2020 [41]	China	Kaempferol, quercetin, 2-methyl-7-methoxy-4'-nitro-isoflavone, naringenin, formononetin	AutoDock, Discovery software, PyMOL software, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, Cytoscape Software	Not applicable (interleukins)	All substances showed energy above -5.00 kcal/mol
Fischer et al. 2020 [97]	Switzerland	Rhamnetin	AutoDock, Maestro Package, Protein Data Bank, VirtualToxLab	Mpro (6LU7)	Rhamnetin presented the best binding energy for Mpro (-8.20 kcal/mol)
Yu et al. 2020 [23]	China	Luteolin	AutoDock, NCBI, RCSB	3CLpro (6LU7), PLpro (4OVZ), RdRP (6NUS) and Spike protein (6VSB)	Luteolin showed the best binding energy for 3 CLpro (-5.37 kcal/mol); for RdRP (-7.80 kcal/mol); for protein spike (-7.00 kcal/mol); for PLpro (-6.80 kcal/mol)
Das et al. 2020 [98]	India	Rutin, hesperidin, epigallocatechin gallate, epigallocatechin, myricitrin, quercitrin, glabridin, rhoifolin, vitexin	SwissDock server, Pymol	Mpro (6Y84)	Rutin presented the best binding energy (-9.55 kcal/mol)

Table 1 (continued)

Author and Year	Country	Flavonoids evaluated	Programs	Target protein and PDB code	Main results
Islam et al. 2020 [99]	Bangladesh	Baicalin, glabridin, cyanidin 3-glucoside, apigenin, quercetin, luteolin	Autodock, Gold software, admetSAR	Mpro (6LU7)	Cyanidin 3-glucoside presented the best binding energy (-8.40 kcal/mol)
Jo et al. 2020 [31]	Republic of Korea	Herbacetin, rhoifolin, pectolinarin, kaempferol, morin	Schrodinger Package (Maestro), PubChem, RCSB	3CLpro (4WY3)	Rhoifolin showed the best binding energy (-9.56 kcal/mol)
Alamri et al. 2020 [28]	Saudi Arabia	Luteolin and kaempferol	Autodock, PyRx, GROMACS Software, SwissParam	RNA polymerase dependent on viral RNA (RdRP) (6M71), 3CLpro (6W63) and papain as protease (PLpro) (6W9C)	Luteolin showed the best binding energy for RdRP (-9.80 kcal/mol)
Dubey and Dubey 2020 [30]	India	Narcissoside	Software Molegro Virtual Docker (MVD), Pubchem	3CLpro (6W63)	Narcissoside showed the best binding energy (-180.74 kcal/mol)
Joshi et al. 2020 [37]	India	Quercetin, Chrysoeriol, delphinidin-3-*O*-glucoside	PharmaGist web servers, Ligplot Software, PubChem, RCSB, DruLiTo software, admetSar	Mpro (6LU7), ACE II (1R4L)	Quercetin showed the best binding energy for Mpro (-8.30 kcal/mol; for ACE II (-11.30 kcal/mol)
Lung et al. 2020 [100]	Taiwan	Theaflavin	Modeller; Chimera, SWISS-MODEL, ZINC15 database, Blind Docking server	RNA-dependent RNA polymerase (RdRP)	Theaflavin showed the best binding energy (-9.11 kcal/mol)
Owis et al. 2020 [101]	Egypt	Kaempferol	DMP, RCSB	Mpro (6LU7)	Kaempferol showed the best binding energy (-8.12 kcal/mol)
Glinsky 2020 [40]	United States	Quercetin	Gene Expression Omnibus (GEO)	ACE II	There was no apply binding energy
Gorla et al. 2021 [25]	India	Biochanin A, silibinin (silybin A), silymarin, malvidin, morin, quercetin and diosmetin	Molegro Virtual Docker, NCBI, RCSB, Swiss ADME software	ACE II (6VW1) and protein spike	Biochanin A showed the best binding energy for protein spike (-78,41 kcal/mol) Silymarin/ silibinin (silybin A) showed the best binding energy for ACE II (- 121.28 kcal/mol)

DMP: Data Management Plan; MOE: Molecular Operating Environment Software; NCBI: National Center for Biotechnology Information; PDB Code: Protein *data bank database code*; PKCSM tool: Prediction of pharmacokinetic and toxicity properties of small molecules using chart-based signatures; RCSB: Architectural advances in search for integrated research and efficient access to data from the macromolecular structure of the PDB file

Quercetin also presented effects on the inhibition of PLpro, according to Fatoki et al. [26] and Kandeel et al. [27] (binding energies of -10.20 kcal/mol and -7.75 kcal/mol, respectively). These results were similar for hesperidin (binding energy of -9.40 kcal/mol) [19] and luteolin (binding energy of -6.80 kcal/mol) [23].

Among the flavonoids with the potential to inhibit 3CLpro, those that showed the best results were amentoflavone, baicalein, cyanidin 3-rutinoside, hesperidin, kaempferol, luteolin, narcissoside, naringin, pectolinarin, quercetin, and rhoifolin [19, 23, 26, 28–34]. In this scenario Narcissoside has the highest binding energy (-180.74 kcal/mol) [30]. On the other hand, epigallocatechin presented binding energy above -12.90 kcal/mol against RdRP [35]. Finally, the most promising flavonoids inhibiting the host's ACE II receptor were cyaniding, delphinidin, orientin, quercetin, silymarin/silibinin (silybin A), and theaflavin monogallate with binding energies varying from -4.76 kcal/mol until -121.28 kcal/mol [20, 21, 24, 25, 35–39].

Three of the studies evaluated for data extraction (Glinsky [40], Ruan et al. [41] Wang et al. [42]) used some flavonoids to build molecular maps guided by genomic regulatory elements by analyzing gene silencing and overexpression experiments. Quercetin was a flavonoid identified as a supposed mitigation agent for COVID-19. There is a change in the expression of human genes encoding SARS-CoV-2 target proteins when, by structural similarity, the flavonoid develops as an inhibitor interfering with the functions of SARS-CoV-2 viral proteins in human cells.

The different binding energy values occurred due to the various programs used in the articles since each program has a different algorithm and formula for calculating energy [43]. Despite the heterogeneity between the methodologies used, ranking the most promising flavonoids was suggested, classified according to the software used, lower binding energy, and the number of targets (Table 2).

The main chemical structures of flavonoids numbered in sequence (1 to 29), are shown bellow in Fig. 2. Being that the flavonoids that were considered as the most promising according to binding energy, were the sequence 1 to 8, as described below. The sequence 9 to 29 are the other flavonoids highlighted, according to the studies included in this review.

Within the different versions of the AutoDock program, the most promising flavonoids are orientin **(1),** whose energy ranged from -90.20 kcal/mol to -70.60 kcal/mol; quercetin **(2)**, ranging from -22.17 kcal/mol to -7.50 kcal/mol; and epigallocatechin **(3)**, with energy of -12.90 kcal/mol. Regarding the number of targets, among the articles included in this review, quercetin **(2)** presented binding energy in six different targets, orientin in three different targets, and epigallocatechin only one target.

Moreover, with the versions of Molegro Virtual Docker software, narcissoside **(4)** showed the lowest energy (-180.74 kcal/mol). In this program, the most promising flavonoids are narcissoside **(4)**, with an energy of -180.74 kcal/mol and silymarin **(5)**, with an energy of -121.28 kcal/mol, both of which were bound to only one type of target. While with the Schrodinger Package, neohesperidin **(6)** had the lowest energy, with -15.83 kcal/mol. In this program, the most promising flavonoids are neohesperidin **(6)**, with -15.83 kcal/mol; delphinidin-3,5-diglucoside **(7)**, with energy ranging from -13.60 kcal/mol to -12.20 kcal/mol; and delphinidin-3-sambubioside-5-glucoside **(8)**, with the lowest energy of -12.37 kcal/mol for only one type of target. In addition to that, appendix D of supplementary material, includes the other chemical structures of the flavonoids (30 to 76) investigated in the studies included in this review.

Discussion

To the best of our knowledge, this is the first comprehensive scoping review to systematically synthesize the available evidence on the potential therapeutic effects of different flavonoids against SARS-CoV-2.

We included 37 articles that refer to in silico models. A recent study design that guides the development of other in vivo and in vitro studies, favoring resource savings and providing insights into the most effective components, speeding up the development process and research direction.

Within molecular mechanics studies, molecules are sets of atoms linked together by harmonic or elastic forces. These have been described as potential energy functions of structural contributions and unbound interactions. When these forces are added together, they form the force field, which can have adjustable parameters to improve the set of properties of the molecule [44, 45].

In this study, we present molecular docking, a molecular modeling method that seeks to predict the structures of receptor-ligand complexes target of interest. The main tools used are the search algorithm and an energy-scoring function. The scoring evaluates the binding energy of interaction between the ligand and the target receptor, classifying the best binding modes interactions between anchored ligands and proteins and predicting possible modes of action or lack thereof. Compounds with lower binding energy may have a higher affinity for target proteins [46, 47].

At the beginning of the pandemic several studies sought to compare the already studied SARS-CoV and the new SARS-CoV-2. Through homology modeling, it was revealed that the Mpro, RdRP, and Spike proteins of SARS-CoV-2 are remarkably similar to SARS-CoV. Thus, anti-coronavirus drug design strategies could be classified through the inhibition of proteins such as Mpro or

Table 2 Classification of energies, programs, and targets

Target	Flavonoid	Binding energy	Program	Author and Year
3 CLpro	Luteolin	-5.37 kcal/mol	AutoDock vina*	Yu et al. 2020
3CLpro	Naringin	-9.70 kcal/mol	AutoDock vina*	Meyer-Almes 2020
3CLpro	Hesperidin	-8.00 kcal/mol	AutoDock vina*	Mahdian et al. 2020
3CLpro	Quercetin	-7.50 kcal/mol	AutoDock vina*	Abian et al. 2020
3Clpro	Quercetin	-8.20 kcal/mol	AutoDock vina v1.1.2	Fatoki et al. 2021
3CLpro	Baicalein	-7.80 kcal/mol	AutoDock vina v1.1.2	Tao et al. 2020
3CLpro	Amentoflavone	-8.49 kcal/mol	AutoDock v4.2	Chitranshi et al. 2020
3CLpro	Narcissoside	-180.74 kcal/mol	Molegro Virtual Docker*	Dubey and Dubey 2020
3CLpro	Rhoifolin	-9.56 kcal/mol	Package Schrodinger software suite (Maestro, version 11.8.012)	Jo et al. 2020
3CLpro	Pectolinarin	-10.97 kcal/mol	Package Schrodinger software suite (Maestro, version 11.8.012)	Jo et al. 2020
3CLpro	Cyanidin 3-rutinoside	-17.02 kcal/mol	MOE (Molecular Operating Environment Software)*	Khalifa et al. 2020
ACE II	Quercetin	-11.30 kcal/mol	AutoDock vina*	Joshi et al. 2020
ACE II	Cyanidin	-8.20 kcal/mol	AutoDock vina*	Joshi et al. 2021
ACE II	Quercetin	-8.40 kcal/mol	AutoDock vina v1.1.2	Tao et al. 2020
ACE II	Orientin	-70.60 kcal/mol	AutoDock v4.2	Alagu et al. 2021
ACE II	Quercetin	-4.41 kcal/mol	AutoDock v4.2	Chikhale et al. 2020
ACE II	Quercetin	-22.17 kcal/mol	AutoDock Raccoon	Pandey et al. 2020
ACE II	Quercetin	-92.05 kcal/mol	Molegro Virtual Docker v3.0.0	Maurya et al. 2020
ACE II	Silymarin	-121.28 kcal/mol	Molegro Virtual Docker v6.0	Gorla et al. 2021
ACE II	Delphinidin-3,5-diglucoside	-13.60 kcal/mol	Glide package of Schrodinger chemical simulation software*	Sharma and Shanavas 2020
ACE II	Theaflavin monogallate	-6.72 kcal/mol	PatchDock web server*	Maiti and Banerjee 2020
Envelope protein	Rutin	-9.30 kcal/mol	AutoDock 4 and vina	Bhowmik et al. 2020
Mpro	Eriodictyol	-9.90 kcal/mol	AutoDock vina*	Joshi et al. 2021
Mpro	Quercetin	-9.90 kcal/mol	AutoDock vina*	Joshi et al. 2021
Mpro	Cyanidin 3-glucoside	-8.40 kcal/mol	AutoDock vina*	Islam et al. 2020
Mpro	Quercetin	-8.30 kcal/mol	AutoDock vina*	Joshi et al. 2020
Mpro	Calophyllolide	-9,30 kcal/mol	AutoDock vina v1.1.2	Vijayakumar et al. 2020
Mpro	Rhamnetin	-8.20 kcal/mol	AutoDock vina v1.1.2	Fischer et al. 2020
Mpro	Hesperetin	-7.90 kcal/mol	AutoDock vina v1.0	Narkhede et al. 2020
Mpro	Orientin	-90.20 kcal/mol	AutoDock v4.2	Alagu et al. 2021
Mpro	Delphinidin-3,5-diglucoside	-12.20 kcal/mol	Glide package of Schrodinger chemical simulation software*	Sharma and Shanavas 2020
Mpro	Delphinidin-3-sambubioside-5-glucoside	-12.37 kcal/mol	Package Schrodinger software suite (Maestro, version 11.6)	Fakhar et al. 2021
Mpro	Rutin	-9.55 kcal/mol	Swissdock*	Das et al. 2020
Mpro	Kaempferol	-8.12 kcal/mol	London dG score*	Owis et al. 2020
PLpro	Hesperidin	-9.40 kcal/mol	AutoDock vina*	Mahdian et al. 2020
PLpro	Luteolin	-6.80 kcal/mol	AutoDock vina*	Yu et al. 2020
PLpro	Quercetin	-10.20 kcal/mol	AutoDock vina v1.1.2	Fatoki et al. 2021
PLpro	Quercetin	-7.75 kcal/mol	Package Schrodinger (Maestro)*	Kandeel et al. 2021
Protein Spike	Quercetin	-8.50 kcal/mol	AutoDock vina*	Pandey et al. 2020
Protein Spike	Hesperidin	-7,40 kcal/mol	AutoDock vina*	Mahdian et al. 2020
Protein Spike	Luteolin	-7.00 kcal/mol	AutoDock vina*	Yu et al. 2020
Protein Spike	Eriodictyol	-7.90 kcal/mol	AutoDock vina v1.1.2	Vijayakumar et al. 2020
Protein Spike	Calophyllolide	-7.90 kcal/mol	AutoDock vina v1.1.2	Vijayakumar et al. 2020
Protein Spike	Orientin	-72.30 kcal/mol	AutoDock v4.2	Alagu et al. 2021
Protein Spike	Quercetin	-86.22 kcal/mol	Molegro Virtual Docker v3.0.0	Maurya et al. 2020

Table 2 (continued)

Target	Flavonoid	Binding energy	Program	Author and Year
Protein Spike	Biochanin A	-78.41 kcal/mol	Molegro Virtual Docker v6.0	Gorla et al. 2021
RdRP	Epigallocatechin	-12.90 kcal/mol	AutoDock vina*	Joshi et al. 2021
RdRP	Luteolin	-7.80 kcal/mol	AutoDock vina*	Yu et al. 2020
RdRP	Theaflavin-3,3'- digallate	-9.90 kcal/mol	AutoDock vina v1.1.2	Singh et al. 2020
RdRP	Luteolin	-9.80 kcal/mol	AutoDock vina v1.1.2	Alamri et al. 2020
RdRP	Quercetin	-9.20 kcal/mol	AutoDock vina v1.1.2	Fatoki et al. 2021
RdRP	Calophyllolide	-8.70 kcal/mol	AutoDock vina v1.1.2	Vijayakumar et al. 2020
RdRP	Theaflavin	-9.11 kcal/mol	Blind Docking server*	Lung et al. 2020
Spike Protein	Fisetin	-8.50 kcal/mol	AutoDock vina*	Pandey et al. 2020
TMPRSS2	Hesperidin	-6.10 kcal/mol	AutoDock vina*	Mahdian et al. 2020
TMPRSS2	Neohesperidin	-66.53 kcal/mol	Glide package of Schrodinger molecular modelling suite (Glide Score)*	Chikhale et al. 2020
TMPRSS2	Neohesperidin	-12.77 kcal/mol	Glide package of Schrodinger molecular modelling suite (Dock Score)*	Chikhale et al. 2020
TMPRSS2	Neohesperidin	-12.77 kcal/mol	Glide package of Schrodinger molecular modelling suite (Prime MM-GBSA)*	Chikhale et al. 2020
Viral peptides	Kaempferol	-6.20 kcal/mol	AutoDock vina*	Hamza et al. 2021

*Version not specified by the authors

enzymes that are necessary for replication and synthesis of viral RNA (RdRP) or inhibition of structural proteins such as the spike protein to adhere to host cells by inhibiting domain 2 of the angiotensin-converting enzyme [48–50].

The replicative cycle of SARS-CoV-2 begins with the interaction of the spike glycoprotein (S) located in the viral envelope, responsible for the crown conformation allocated to the Coronaviridae family, with the cell receptor of the angiotensin-converter enzyme 2 (ACE II), located on the surface of the target cell. The link between glycoprotein ACE II is responsible for the tropism of the virus by the host cell [51, 52].

After the adoption and penetration stages, denudation occurs, in which there is the release of the genetic material (RNA) of the virus in the cytoplasm of the host cell. The virus carries the viral proteins that are necessary for its initial survival in the target cell, involved in the process of transcription and viral replication (e. g. nucleocapsid contains papain-type viral proteases (PLpro), chymotrypsin proteases (3CLPro, also called MPro), in addition to RNA-dependent RNA polymerase, helicase, and RNA replicase) [53, 54].

The replication strategies of a β-coronavirus are based on the initial translation of genomic RNA into a precursor polyprotein, which is processed into non-structural proteins. Thus, genomic RNA is used as a mold by an RNA-dependent viral replication (RdRP) for the complete transcription of a simple negative RNA tape, serving as a template for the transcription of subgenomic messenger Rs RNA used to encode viral structural proteins and transcribing new genomic RNA, originating new viruses [55].

Flavonoids are phenolic compounds subdivided into different groups, including flavonols, flavones, flavanones, catechins, anthocyanins, isoflavones, dihydrophenols, and chalcones. These natural products are known to have antiviral activity, acting mainly on the viral DNA polymerase enzyme and having hydroxyl groups that favor interactions with crucial residues. Additionally, the position and number of hydrogen bonds are essential in the analysis of the inhibitory potential against the SARS-CoV-2 virus due to their binding affinity and amino acid interactions (glycine, alanine, serine, histidine, asparagine, glutamine, cysteine, proline, tyrosine, arginine, aspartic acid, glutamic acid, phenylalanine, valine, tryptophan, threonine, lysine, leucine, isoleucine, and methionine) [56].

Within the viral cycle, the SARS-CoV-2 replication mechanism was primarily led by RdRP, a complex of non-structural proteins [57, 58]. Viral RNA is translated into various polyproteins by the main protease (Mpro) action on SARS-CoV-2. In molecular modeling, the removal/mutation of the amino acids presented in each target, showed the loss of Mpro activation and reversion to the protomer form as well as the spike (S) protein, which attacks human angiotensin-converting enzyme 2 receptors [59–61]. The human equivalent for this particular protease is absent, making this a safe target for anti-SARS-CoV-2 agents.

Figure 3 shows the most promising targets and flavonoids obtained from the 37 studies analyzed, according to our research on the reproductive cycle of SARS-CoV-2.

The search for new substances to treat a disease, and even a new condition, is based on the search for articles that present some confirmation of substances that promoted positive

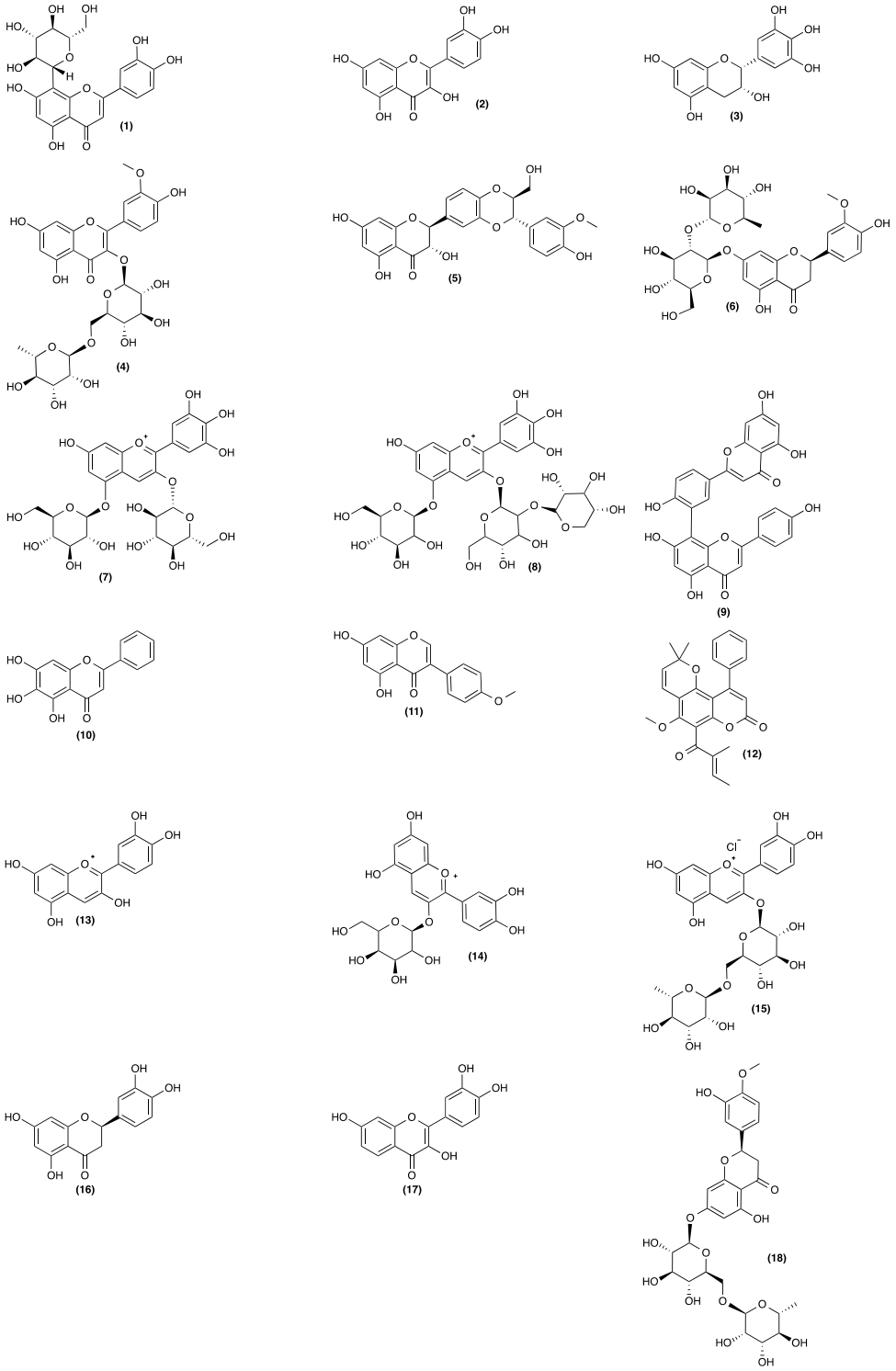
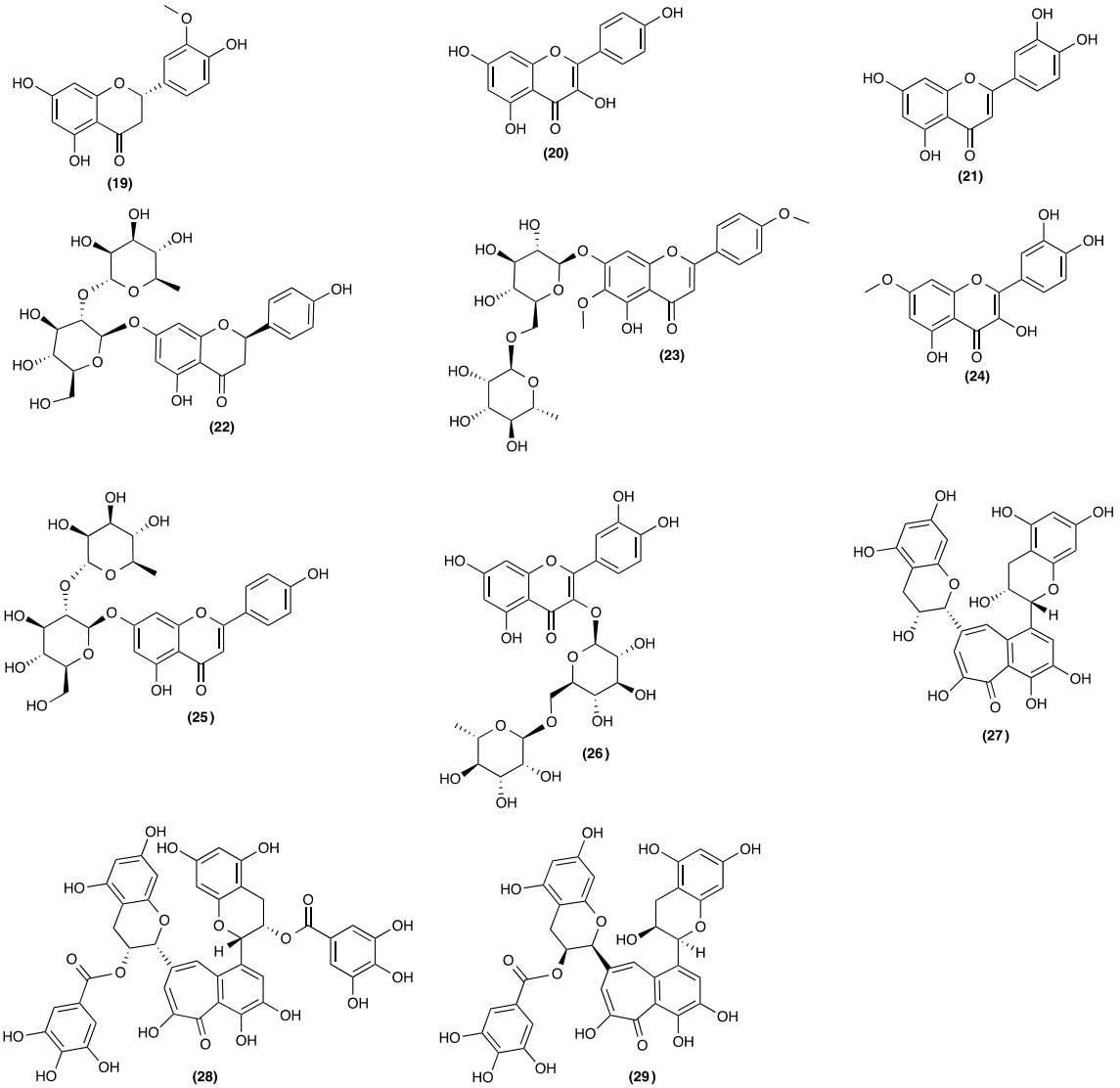


Fig. 2 Chemical structures described in the most promising results of the 37 in silico studies drawn by ChemDraw version 14.0.0.118. The chemical structures of flavonoids mentioned, correspond to: (1) orientin; (2) quercetin; (3) epigallocatechin; (4) narcissoside; (5) silymarin; (6) neohesperidin; (7) delphinidin-3,5-diglucoside; (8) delphinidin-3-sambubioside-5-glucoside; (9) amentoflavone; (10) baicalein; (11) biochanin A; (12) calophyllolide; (13) cyanidin; (14) cyanidin-3-glucoside; (15) cyaniding-3-rutinoside; (16) eriodictyol; (17) fisetin; (18) hesperidin; (19) hesperitin; (20) kaempferol; (21) luteolin; (22) naringin; (23) pectolinarin; (24) rhamnetin; (25) rhoifolin; (26) rutin; (27) theaflavin; (28) theaflavin-3,3'- digallate; (29) theaflavin monogallate

effects in similar diseases. Thus, this work shows research and studies with flavonoids that had a positive influence on diseases similar to SARS-CoV-2, influencing the development of in silico studies, and through the promising results, encourage the research of these flavonoids for in vitro and in vivo studies.

Among all the flavonoids, compounds from the flavones class were the first to be associated with antiviral properties. In the late 1940s, quercetin was described as having a "prophylactic effect" against the rabies virus in infected rats [62]. We found this compound with promising activity against SARS-CoV-2 (energies ranging from -4.41 to -92.05 kcal/

Fig. 2 (continued)



mol). Previous studies show quercetin can bind with glycoproteins from the viral envelope and cellular receptors by modifying their chemical structure and blocking the virus-binding site. Brum et al. [63] demonstrated a reduction in the virucide activities of some viruses with this substance, while Carvalho et al. [64] confirmed its effects against canine parvovirus in vitro studies.

Other flavonoids, such as rutin, amentoflavone, baicalein, myricitrin, and kaempferol are also related to antiviral activity, respectively, against HIV, herpes simplex, human cytomegalovirus, African swine fever, and influenza A, H1N1 and H9N2 [62, 65]. In the review study by Khazdair et al. [14], it was shown in research results that kaempferol suppresses the activity of influenza viruses, such as H1N1 and H9N2, and shown greats results for in vitro studies for hepatitis B virus, in addition, to presenting other in vitro study, where MH-S cells infected by the H9N2 influenza viruses were treated with kaempferol (50 mM) and this significantly reduced the accumulation of ROS, malondialdehyde, TNF-α, IL-1β, and IL-6. In another dosage, 100 µmol/L,ç completely inhibited the replication of bovine herpesvirus 1 in Madin-Darby bovine renal cells.

Still in the review study by Khazdair et al. [14], in an in vivo study, kaempferol at a dosage of 15 mg/kg reduced pulmonary edema, wet/dry lung weight, myeloperoxidase activity, pulmonary capillary permeability, and the number of inflammatory cells in mice infected with kaempferol. H9N2 influenza virus. For SARS-CoV, he demonstrated that there is potency to block a cation-selective channel that is expressed in the infected cell.

When quercetin and kaempferol are joined, there is a binding to the proteins of SARS-CoV2, which is involved in inflammatory responses and the modulation of the immune system through modification in the expression of cyclooxygenase 2, interleukins, MAPKs, alteration of the signaling cascade [14].

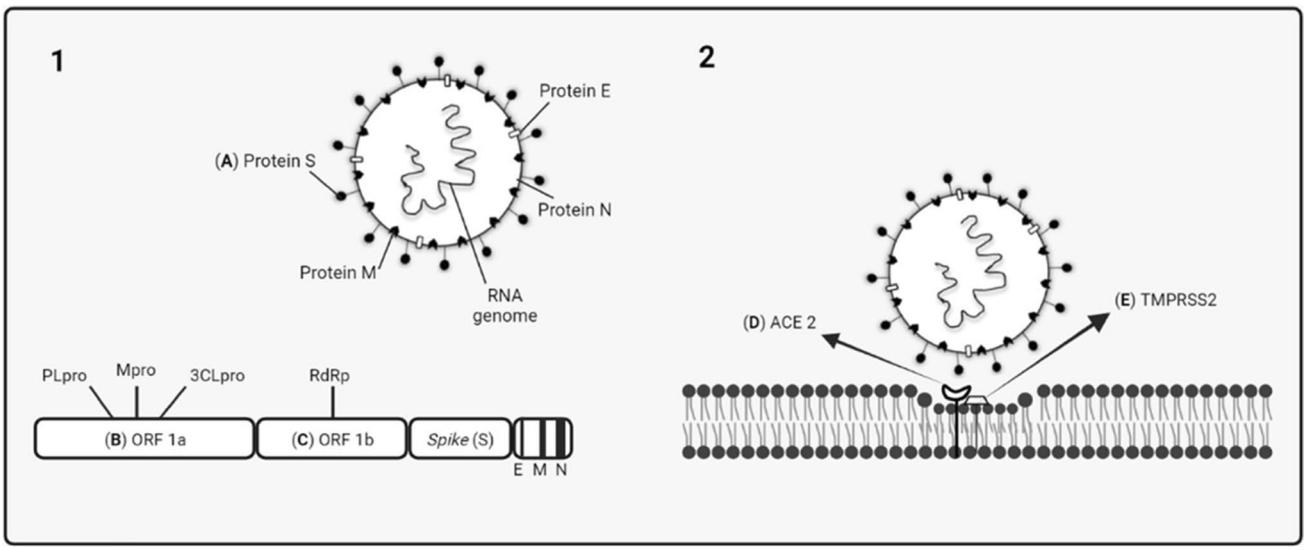


Fig. 3 SARS-CoV-2 life cycle in the main flavonoids discuss in the scoping review. ***1****. Shows the main structural and non-structural target proteins of SARS-CoV-2 discussed in the review. The most promising flavonoids analyzed* in silico *study for (**A**) protein S were quercetin, eriodictyol, hesperidin, calophyllolide, fisetin, orientin, luteolin, and biochanin A; (**B**) ORF 1a (PLpro) were quercetin, eriodictyol, hesperidin, and luteolin; (**B**) ORF 1a (Mpro) were rutin, kaempferol, delphinidin-3-sambubioside-5-glucoside, quercetin, eriodictyol, calophyllolide, delphinidin-3,5-diglucoside, orientin, rhamnetin, and cyanidin-3-glucoside; (**B**) ORF 1a (3CLpro) were amentoflavone, quercetin, hesperidin, naringin, pectolinarin, cyanidin-3-rutinoside, baicalein, luteolin, rhoifolin, and narcissoside; (**C**) ORF 1b (RdRP) were quercetin, epigallocatechin, calophyllolide, theaflavin-3,3'-digallate, luteolin, and theaflavin. In **2**, the main cellular targets discussed in this study are shown, being (**D**) ACE 2 and (**E**) TMPRSS2, and the flavonoids observed for these targets were for (**D**) quercetin, cyanidin, theaflavin monogallate, delphinidin-3,5-diglucoside, orientin, and silymarin/Silibinin (silybin A); and for (**E**)* neohesperidin, hesperidin

Rutin promotes the normalization of resistance and permeability of the wall of lymphatic and venous vessels. In studies conducted on guinea pig ileum, this compound acted as a non-competitive inhibitor of ACE II and prostaglandin E2 [66], which may justify its antiviral effect, including against SARS-CoV-2. Myricitrin has recently been associated with activities against HIV, influenza, and leukemia [67]. The flavone baicalein from Scutellaria baicalensis Georgi (Lamiaceae) has been described as an anti-HIV compound, as it leads to a dose-dependent inhibition of both the HIV-1 protein and reverse transcriptase. It also interferes with the interaction between viral envelope proteins and CD4 + cells, thus reducing the virus binding capacity to the host cell [68, 69].

Orientin, a flavonoid from the Trollius chinensis Bunge (Ranunculaceae) flowers, is currently used in treating respiratory tract infections in Asian countries [70]. This compound could be a promising alternative against COVID-19 as it inhibits the spike protein. We also found the compound luteolin with high binding energy against several SARS-CoV-2 targets (e.g., PLpro, 3CLpro, RdRP, ACE II), which could be further investigated in future trials. This substance inhibits the activation of T cells and the release of inflammatory cytokines by microglia [71].

Some anthocyanins previously demonstrated antioxidant and anti-inflammatory properties (e.g., inhibition of LDL oxidation) and the potential to decrease the risk of cardiovascular diseases and cancer [72–76]. Compounds such as phacelianin and cyanidin additionally have anti-mutagenic and antiviral activities [77–79].

The delphinidins – i.e., delphinidin-3,30-di-glucoside-5-(6-p-coumarylglucoside) and delphinidin-3,5-diglucoside – act on platelet activity by decreasing the expression of activated αIIβ3 integrin on platelets, inhibiting the platelet aggregation in trials with agonists ADP (Adenosine Diphosphate) and TRAP (Thrombin Receptor Activator Peptide) thrombin agonist, which contributes to the prevention of thrombosis. Additionally, they may improve some endothelial functions by increasing nitric oxide synthesis and reducing platelet aggregation. Other effects of these substances include hepatic protection, antitumor, and anti-inflammatory vascular effects [80, 81].

Compounds such as gallocatechin and neohesperidin (dihydrochalcones class) have proved antioxidant activity similar to vitamin C and vitamin E. Thus, they can strengthen the immune system and help inhibit the action of free radicals, especially in the cardiovascular system [82, 83].

Among the flavanones, hesperidin may play a significant role in the human system as an anti-inflammatory, since it inhibits both the cyclooxygenase (COX) and lipoxygenase pathways [84, 85]. Its anti-inflammatory effects are

additionally associated with the inhibition of the synthesis of prostaglandins (PGE2 and PGE2a) [86]. Other substances of this class, such as naringin, also present protective effects on several systems (i.e., renal, cardiovascular, hepatic, intestinal microbiota, and immunological) due to their biological properties as antioxidant, antitumor, antiviral, antibacterial, anti-inflammatory, antiadipogenic, and cardio-protective [87].

Among the isoflavones, formononetin presents an important activity against ACE II and 3CLpro. This substance has anti-inflammatory and antioxidant action through the decrease in the formation of free radicals, preventing lipid peroxidation [88], including in the central nervous system [89].

The study by Kaul et al. [15] shows in their review that several in vitro studies explored the anti-SARS-CoV-2 action of flavonoids through the guidance of in silico studies associated with additional in vitro or in vivo investigations of anti-SARS-CoV and anti-MERS-CoV activities of various flavonoids studied. It is also cited from 2021 studies with clinical trials in patients with COVID-19 showing the promising effect of quercetin.

Computational molecular modeling precedes in vitro and in vivo studies, demonstrating great possibilities of interaction through molecular docking between compounds and the molecular target [90].

In summary, all the studies used virtual molecular docking models to verify the affinity of compounds from the flavonoid class with crucial proteins in the replication cycle of the SARS-CoV-2 virus (Spike protein, PLpro, 3CLpro/MPro, RdRP, and inhibition of the host's ACE II receptor). The flavonoids that showed the lowest binding energies and more targets were orientin, quercetin, epigallocatechin, narcissoside, silymarin, neohesperidin, delphinidin-3,5-diglucoside, and delphinidin-3-sambubioside-5-glucoside.

This study has some limitations. No statistical synthesis of the evidence (i.e., employing meta-analysis) was possible since the heterogeneity between studies (e.g., study design and methods used/programs, type of flavonoid, outcome measure) is very high. Thus, other natural compounds (alone or combined) may have some impact in this context and should be better evaluated in other studies. The focus of this review was on the antiviral effects of flavonoids.

Conclusion

In silico models demonstrated that some flavonoids showed the lowest binding energies and most numbers of targets (ranging from three to six), such as orientin, quercetin, epigallocatechin, narcissoside, silymarin, neohesperidin, delphinidin-3,5-diglucoside, and delphinidin-3-sambubioside-5-glucoside, and they showed promising antiviral activities against SARS-CoV-2 through different mechanisms of action.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s40199-023-00461-3.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest in relation to the data presented in this publication.

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