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Flavonoides como possíveis alvos terapêuticos contra a doença do coronavírus (COVID-19): uma revisão de escopo

LARISSA TOIGO

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Estadual Oeste do Paraná, *campus* de Cascavel, em cumprimento parcial aos requisitos para obtenção do título de Mestre em Ciências Farmacêuticas na linha de pesquisa de fármacos e medicamentos.

Orientadora: Profª. Drª. Andreia Cristina Conegero Sanches
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BIOGRAFIA RESUMIDA

Larissa Toigo, natural de Cascavel, Paraná, Brasil, nascida em 20 de setembro de 1993, graduou-se em Farmácia, turma XVI (2013 - 2018), pela Unioeste em 11 de fevereiro de 2019. Trabalha como motorista de van escolar, desde 04 de fevereiro de 2019, em Cascavel. Em março de 2020 iniciou as atividades como aluna do Programa de Pós-Graduação *Stricto Sensu* em Ciências Farmacêuticas e desenvolve projeto experimental de dissertação junto à linha de pesquisa de fármacos e medicamentos, orientada pela Profª. Drª. Andreia Cristina Conegero Sanches.

‘‘Os sonhos não determinam onde vocês vão chegar, mas produzem a força necessária para tirá-los do lugar em que vocês estão. Sonhem com as estrelas para que vocês possam pisar pelo menos na lua. Sonhem com a lua para que vocês possam pisar pelo menos nos altos montes. Sonhem com os altos montes para que vocês possam ter dignidade quando atravessarem os vales das perdas e frustrações’’.

Augusto Cury

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Dedico esta dissertação de conclusão de mestrado aos meus pais, por terem me ensinado os valores de formação de um bom caráter, imprimindo em minha formação o conceito de luta e busca pelos objetivos que pretendo alcançar, e ao meu marido por me incentivar a permanecer no caminho que meus pais me ensinaram a trilhar.

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Flavonoides como possíveis alvos terapêuticos contra a doença do coronavírus (COVID-19): uma revisão de escopo

RESUMO

Esta revisão de escopo visa apresentar os efeitos promissores e os possíveis alvos dos compostos flavonoides sobre potenciais alvos terapêuticos no processo de infecção por SARS-CoV-2. As bases de dados eletrônicas *PubMed* e *Scopus* foram pesquisadas por estudos que avaliaram o desempenho de substâncias da classe dos flavonoides em diferentes alvos virais da infecção por SARS-CoV-2. A estratégia de busca recuperou 382 artigos, após a exclusão de duplicatas. Durante o processo de triagem, 265 estudos foram considerados irrelevantes. Ao final da avaliação do texto completo, 37 estudos foram considerados elegíveis para extração de dados e síntese qualitativa. Todos os estudos utilizaram modelos de *docking* molecular virtual para verificar a afinidade de compostos da classe dos flavonoides com proteínas-chave no ciclo de replicação do vírus SARS-CoV-2 (proteína *Spike*, PLpro, 3CLpro/MPro, RdRP e inibição do receptor da ECA 2 do hospedeiro, nos estudos *in sílico*). Estudos sobre a proteína *Spike* avaliaram um total de 26 flavonoides diferentes, sendo os mais promissores: biochanina A (-78,41 kcal/mol); calofilolide e eriodictiol (-7,90 kcal/mol); fisetina (-8,50 kcal/mol); hesperidina (-7,4 kcal/mol); quercetina (-86,22 kcal/mol); luteolina (-7,00 kcal/mol); orientina (-72,30 kcal/mol). Na inibição da PLpro, a quercetina apresentou as energias de ligação de -10,20 kcal/mol e -7,75 kcal/mol. A hesperidina teve energia de ligação de -9,40 kcal/mol e luteolina com energia de ligação de -6,80 kcal/mol. Dentre os flavonoides com potencial para inibir 3CLpro, os que apresentaram os melhores resultados foram amentoflavona, baicaleína, cianidina 3-rutinosídeo, hesperidina, campferol, luteolina, narcisosídeo, naringina, pectolinarina, quercetina e rhoifolina. O narcisosídeo tem a maior energia de ligação -180,74 kcal/mol, a epigalocatequina apresentou energia de ligação acima de -12,90 kcal/mol contra RdRP e os flavonoides mais promissores que inibem o receptor ECA 2 do hospedeiro foram cianeto, delfinidina, orientina, quercetina, silimarina/silibinina (silibina A) e monogalato de teaflavina com energias de ligação variando de -4,76 kcal/mol a -121,28 kcal/mol. Os flavonoides que apresentaram as menores energias de ligação e maior número de alvos foram orientina, quercetina, epigalocatequina, narcisosídeo, silimarina, neohesperidina, delfinidina-3,5-diglicosídeo e delfinidina-3-sambubiosídeo-5-glicosídeo. Esses estudos nos permitem fornecer uma base para ensaios *in vitro* e *in vivo* para auxiliar no desenvolvimento de medicamentos para o tratamento e/ou prevenção da doença causada pelo coronavírus (COVID-19).

Palavras-chave: Coronavírus; Síndrome Respiratória; Plantas medicinais; Bioativos; *In sílico*.

Flavonoids as possible therapeutic targets against coronavírus disease (COVID-19): a scoping review

ABSTRACT

This scoping review aims to present the promising effects and possible targets of flavonoid compounds on potential therapeutic targets in the SARS-CoV-2 infection process. The PubMed and Scopus electronic databases were searched for studies that evaluated the performance of substances from the flavonoid class on different viral targets of SARS-CoV-2 infection. The search strategy retrieved 382 articles after deleting duplicates. During the screening process, 265 studies were considered irrelevant. At the end of the full-text evaluation, 37 studies were considered eligible for data extraction and qualitative synthesis. All studies used virtual molecular docking models to verify the affinity of compounds of the flavonoid class with key proteins in the replication cycle of the SARS-CoV-2 virus (Spike protein, PLpro, 3CLpro/MPro, RdRP and host ACE 2 in in silico studies). Studies on Spike protein evaluated a total of 26 different flavonoids, the most promising being: biochanin A (-78.41 kcal/mol); calofilolide and eriodictiol (-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). In the inhibition of PLpro, quercetin presented binding energies of -10.20 kcal/mol and -7.75 kcal/mol. Hesperidin had a binding energy of -9.40 kcal/mol and luteolin had a binding energy of -6.80 kcal/mol. Among the flavonoids with the potential to inhibit 3CLpro, those with the best results were amentoflavone, baicalein, cyanidin 3-rutinoside, hesperidin, kaempferol, luteolin, narcisoside, naringin, pectolinarin, quercetin and rhoifolin. Narcisoside has the highest binding energy -180.74 kcal/mol, epigallocatechin showed binding energy above -12.90 kcal/mol against RdRP and the most promising flavonoids that inhibit the host ACE 2 receptor were cyanide, delphinidin , orientin, quercetin, silymarin/silibinin (silybin A) and theaflavin monogallate with binding energies ranging from -4.76 kcal/mol to -121.28 kcal/mol. The flavonoids that presented the lowest binding energies and the highest number of targets were orientin, quercetin, epigallocatechin, narcisoside, silymarin, neohesperidin, delphinidin-3,5-diglycoside and delphinidin-3-sambubioside-5-glycoside. These studies allow us to provide a basis for in vitro and in vivo trials to assist in the development of drugs for the treatment and/or prevention of coronavirus disease (COVID-19).

Keywords: Coronavirus; Respiratory Syndrome; Medicinal Plants; *Bioactives; In sílico*.

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LISTA DE SÍMBOLOS E ABREVIATURAS

3CLpro: Protease do tipo quimiotripsina

ECA 2/ ACE 2: Enzima conversora de angiotensina 2

COVID-19: Doença do coronavírus 2019 (*Coronavirus Disease* 2019)

HIV: Vírus da imunodeficiência humana (*human immunodeficiency virus*)

MERS-CoV: Síndrome Respiratória do Oriente Médio (coronavirus Middle East respiratory syndrome)

Mpro: Proteína principal

PLpro: Protease viral tipo papaína

RdRp: RNA polimerase dependente de RNA

SARS-CoV-1: Síndrome respiratória aguda grave do coronavírus 1 (coronavirus severe acute respiratory syndrome 1)

SARS-CoV-2: Síndrome respiratória aguda grave do coronavírus 2 (coronavirus severe acute respiratory syndrome 2)

TMPRSS2: Protease serina transmembranar 2

1. INTRODUÇÃO

A doença do coronavírus 2019 (*Coronavirus Disease* 2019 - COVID-19) é uma doença viral causada pela nova síndrome respiratória aguda grave do coronavírus (SARS-CoV-2), que rapidamente se transformou em uma pandemia. Como se tornou uma grande ameaça à saúde pública global, o desenvolvimento do tratamento tornou-se crucial, e a corrida para encontrar uma cura mobilizou pesquisadores de todo mundo (CUI *et al*, 2020).

No Brasil, a média de casos mantém a tendência de queda. Segundo dados do dia 04 de agosto de 2022, os novos casos somaram 34.240, sendo já 679.594 óbitos e 33.961.568 casos notificados desde o início da pandemia. No mundo, o registro chegou a 582.228.135 diagnósticos de infecção por SARS-CoV-2 e 6.413.836 óbitos por COVID-19 de acordo com os dados do *Coronavírus Resource Center*, da Johns Hopkins University (MEDSCAPE, 2022).

Segundo o Boletim InfoGripe Fiocruz, a região norte do Brasil apresenta crescentes casos de SARS-CoV-2, e na maioria dos estados do sudeste, centro-oeste e sul há uma manutenção na queda desse quadro (MEDSCAPE, 2022).

Diante disso, produtos naturais, como flavonoides e outros, podem ser recursos importantes no desenvolvimento do tratamento coadjuvante de COVID-19, pois já contribuíram para o tratamento de outros vírus, como HIV, MERS-CoV e influenza. O tratamento é baseado principalmente no controle dos sintomas e na inibição da replicação viral, e tem sido objeto de estudo e análise por todo mundo, como por exemplo, as medicações, Paxlovid (antiviral específico para o COVID – 19), Glicocorticóides (anti-inflamatório), Tocilizumab (anticorpo monoclonal), Niclosamida e Ivermectina (antiparasitários). Além disso, a prevenção por meio de medidas sociais pode limitar a transmissão (YANG *et al*, 2020; MEDSCAPE, 2022).

Em 2003, houve um surto semelhante ao COVID-19, porém não de forma pandêmica, mas de semelhante família viral, o SARS-CoV-1, no qual, várias fontes naturais de origem animal e vegetal foram testadas quanto à atividade anti-SARS-CoV-1 e usadas para apoiar o desenvolvimento de medicamentos. Esses metabólitos naturais incluíram flavonoides, flavonois, ácidos graxos, taninos, terpenos e alcaloides. Esses produtos naturais são fonte de substâncias biologicamente ativas, que são muito pesquisadas ao desejar um

direcionamento para tratar algo desconhecido, algo novo, como no caso da pandemia da COVID – 19 (WEN *et al*, 2007).

Vários dos metabólitos naturais anti-SARS-CoV-1 também tem outras atividades biológicas contra outros tipos de vírus ou doenças. Por exemplo, a esponja marinha *mycalamide A* e seu análogo *mycalamide B*, têm atividade biológica contra o Herpes vírus. Ao mesmo tempo, o flavonoide miricetina tem atividade antiviral contra leucemia, HIV e vírus influenza. Além disso, a licorina é famosa por sua ampla gama de aplicações farmacêuticas como antioxidante, antibacteriano, antitumoral, antiinflamatório e anticâncer (DONIA & HAMANN, 2003; ZAKARYAN *et al*, 2017; KHALIFA *et al*, 2018).

Da história de luta contra o SARS-CoV-1, pode-se verificar que os produtos naturais têm grande potencial no tratamento do coronavírus. Wen *et al.* (2007) provaram que os metabólitos naturais, ferruginol, 8β-hidroxiabiet-9, 13-dien-12-ona, 7β-hidroxidesoxiccriptaponol, 3β, 12-diacetoxiabiet-6, 8,11,13-tetraeno, ácido betunólico e savinina representaram atividades biológicas extraordinárias e comprovaram que o tratamento SARS-CoV-1 pode ser avaliado de forma sustentável. Além disso, a avaliação de sua estrutura molecular e mecanismo de inibição pode fornecer suporte inovador para o desenvolvimento de medicamentos (WEN *et al*, 2007).

Os diterpenos do tipo abietano são metabólitos que podem ser encontrados na família das angiospermas de coníferas, como Araucariaceae, Cupressaceae, Phyllocladaceae, Asteraceae e Lamiaceae. Estes possuem mais de 200 compostos com atividades biológicas incluindo antiúlcera, antitumoral, antiinflamatória, antidiabética, antimicrobiana, antileishmania, antimalárica e cardioproteção. Além do grande número de compostos biologicamente ativos, as dibenzilbutirolactonas também possuem atividade antiviral. Exemplos desta categoria estrutural são savinina e hinocinina, que são ativos contra o SARS-CoV-1 e o HIV, respectivamente (WEN *et al*, 2007).

O desenvolvimento de produtos naturais biologicamente ativos para doenças específicas, como COVID-19, ainda é uma tarefa difícil devido à diversidade dos metabólitos naturais, sua complexidade química e poder de extração. Para encurtar o tempo na triagem fitoquímica de vários extratos de produtos naturais, utiliza-se a triagem virtual de compostos biologicamente

ativos, conhecida como análise *in silico* por acoplamento molecular (ELFIKY, 2020; HAI ZHANG *et al*, 2020; JOSHI *et al*, 2020).

A metodologia *in silico* utiliza técnicas computacionais de modelagem molecular. É uma das ferramentas mais utilizadas para o estudo e desenvolvimento de novos fármacos ou para o reposicionamento de fármacos antigos. A modelagem molecular é definida como a investigação das estruturas e propriedades moleculares das substâncias de interesse, por meio de química computacional e técnicas de visualização gráfica. Isso permite construir modelos químicos ou biológicos, que são submetidos a programas computacionais específicos, para visualizar, simular e interpretar sistemas inter-relacionados, como os envolvidos na interação droga-receptor. Esses métodos combinados têm a vantagem de orientar um desenvolvimento mais assertivo de medicamentos e a possibilidade de reduzir o desperdício de tempo e investimentos em moléculas com baixo potencial terapêutico (HENCKEL & BILLINGS, 1995; SANT´ANNA, 2002; SINGH *et al*, 2006; EKINS *et al*, 2007; CZODROWSKI *et al*, 2009).

Desde 1990 a prática baseada em evidência (PBE) tem sido importante instrumento para a tomada de decisões clínicas, programáticas e políticas. Com o crescimento da produção e a busca de conhecimento sistematizado, houve aumento de publicações de revisões da literatura. A Prática Baseada em Evidências é definida como uma abordagem que associa a melhor evidência científica disponível, com a experiência clínica e a escolha do paciente para auxiliar na tomada de decisão. Seu uso, pelos profissionais da saúde, configura-se como uma forma coerente, segura e sistematizada para prover maior qualidade na assistência e a otimização dos recursos, alcançando a eficácia e a relação custo-benefício da prestação de cuidados em saúde. Sua utilização permite diminuir as distâncias entre a pesquisa e a prática assistencial, pois sua implementação ocorre por meio da avaliação dos resultados obtidos das pesquisas, a partir da busca e avaliação crítica das evidências (SACKETT *et al.,* 2003; PEREIRA *et al.,* 2012; SAUNDERS & VEHVILAINEN-JULKUNEN, 2017).

A revisão de escopo tem se destacado mundialmente na área de síntese de evidências em saúde, com notável crescimento a partir de 2012, sendo utilizada para a realização de mapeamento da literatura num determinado campo de interesse, sobretudo quando revisões acerca do tema ainda não foram

publicadas. A revisão de escopo é adequada a tópicos amplos, podendo reunir vários desenhos de estudos e tem a finalidade de reconhecer as evidências produzidas, não classifica a robustez da evidência, mas rastreia e/ou antecipa potencialidades, o que deve apoiar pesquisadores na área e, em certa medida, os trabalhadores de saúde, gestores e formuladores de políticas de saúde (ARKSEY & O'MALLEY, 2005; GRANT & BOOTH, 2009; JBI, 2015; TRICCO *et al.,*2018).

Quase 45 dias após o início da pandemia de COVID-19, em março de 2020, metabólitos naturais de diferentes classes químicas mostraram dados promissores sobre acoplamento molecular virtual. Apesar da estrutura molecular única, várias classes químicas, como flavanonas, flavonóis, alcalóides, ácidos graxos, quinonas, terpenos e esteroides apresentaram energia de ligação ou pontuação de acoplamento semelhantes aos medicamentos reaproveitados (ex: remdesivir e cloroquina) com proteínas envolvidas no COVID-19, incluindo a enzima conversora de angiotensina 2 (ECA 2), protease do tipo quimiotripsina (3CLpro) e protease serina transmembranar 2 (TMPRSS2). O foco da maioria das avaliações de acoplamento está nos inibidores da ECA 2, que é a primeira descoberta relacionada à replicação de COVID-19 e possível resultado da implicação dessa enzima na formação do grupo de risco (FANG *et al*, 2020; YANG *et al,* 2020).

Como o ECA 2 foi indicado como o principal receptor do vírus SARS-CoV-2 em humanos, o foco dos estudos baseia-se na sua regulação como forma de tratamento desse vírus, pois a maioria dos pacientes com COVID-19 confirmou que apresentavam formas graves ou fatais da infecção por conta das comorbidades, principalmente hipertensão ou diabetes (WANG *et al*, 2020; ZHANG *et al,* 2020).

Vários produtos naturais, como a rutina, formononetina e isoflavona, têm atividade inibitória da ECA 2 e são amplamente usados em estudos etnobotânicos e, podem estar presentes na dieta humana. Produtos biológicos (inibidores do ECA 2) são amplamente utilizados, principalmente porque as substâncias sintéticas (enalapril) foram desenvolvidas a partir de metabólitos naturais (BARBOSA-FILHO *et al*, 2006; DASKAYA-DIKMEN *et al,* 2017).

Existem pelo menos 300 plantas com atividade inibidora do ECA 2, incluindo algumas espécies medicinais e alimentares bem conhecidas, como canela (*Cinnamomum zeylanicum* ou *Cinnamomum verum*), pimenta (*Capsicum* spp.), azeitona (*Olea europaea*), espinheiro-alvar (*Crataegus pinnatifida*), erva-moura (*Solanum nigrum*), maracujá (*Passiflora edulis*) e uva (*Vitis vinifera*) (BARBOSA-FILHO *et al*, 2006; PATTEN *et al*, 2016; JOSHI *et al*, 2020).

Embora o primeiro estudo *in silico* de produtos naturais anti-COVID-19 enfatize flavanonas com distribuição mais baixa na flora, como naringina e naringenina, descobertas recentes indicam que derivados glicosilados da quercetina têm boa atividade inibitória. Esses flavonóides, descritos por Joshi *et al.* (2020) incluem quercetina-3-glicuronídeo-7-glicosídeo e quercetina 3-vicianosídeo, que podem ser encontrados na pimenta longa indiana (*Piper longum*), açafrão-da-terra (*Curcuma longa*) e absinto (*Artemisia absinthium*). A silibina é um dos principais metabólitos obtidos das sementes de cardo-leiteiro (*Silybum marianum*), planta tradicionalmente utilizada como quimiopreventivo, antiinflamatório e no tratamento de distúrbios digestivos (GAZAK *et al*, 2007; JOSHI *et al*, 2020).

A despeito do acoplamento molecular também mostrar que é uma estratégia para o tratamento de COVID-19, a pesquisa sobre inibição da protease serina transmembranar 2 (TMPRSS2) é a mais baixa entre as principais proteínas de replicação. O TMPRSS2 é conhecido por seu envolvimento na inoculação e replicação do vírus influenza, câncer e SARS-CoV-1. Os inibidores naturais de TMPRSS2 incluem flavonoides, terpenos e peptídeos. Por exemplo, os flavonoides baicaleína e baicalina, foram relatados como reguladores negativos da expressão de TMPRSS2 em estudos *in silico* contra COVID-19. Vale ressaltar que a baicaleína foi proposta por estudos de acoplamento molecular para ser também um inibidor da ECA 2. O método ideal é interagir os metabólitos com diferentes sítios de ligação viral para aumentar sua possível atividade biológica *in vivo* (CHEN *et al*, 2005; XU *et al*, 2017; OO *et al*, 2019; CHENG *et al*, 2020; HOFFMANN *et al*, 2020; JOSHI *et al,* 2020).

A principal fonte natural de baicaleína são os gêneros *Scutellaria* e *Oroxylum*, existente nas raízes de *S. baicalensis* e nas

sementes de *Oroxylum indicum* (Ababangai). Ambos os flavonoides possuem propriedades terapêuticas como neuroprotetoras, antioxidantes, antiinflamatórias, protetoras renais e anticâncer. Além disso, esses flavonoides também apresentaram atividade como inibidores de vírus, como o Zika vírus (OO *et al*, 2019; GURUNG *et al*, 2020; RAHMAN *et al,* 2020).

A inibição da protease tipo quimiotripsina (3CLpro) no SARS-CoV-2 tem recebido mais atenção dos pesquisadores porque pode impedir a inoculação do vírus no hospedeiro (CUI *et al*, 2020; GENTILE *et al*, 2020; GURUNG *et al*, 2020)

Khaerunnisa *et al.* (2020) avaliaram os metabolitos naturais que podem inibir SARS-CoV-2 por acoplamento molecular, através da inibição do 3CLpro, enfatizando os resultados proeminentes de caempferol, quercetina, luteolina-7-glicosídeo, desmetoxicurcumina, naringenina, apigenina-7-glicosídeo, oleuropeína, catequina, curcumina e epigalocatequina. A atividade anti-SARS-CoV-2 desses flavonoides é vantajosa porque eles são facilmente encontrados e estão bem distribuídos em famílias de plantas angiospermas, incluindo Lauraceae, Lamiaceae, Apiaceae e Leguminosae (ZAKARYAN *et al*, 2017; GENTILE *et al*, 2020; JOSHI *et al*, 2020).

Além dos resultados promissores observados para os flavonoides, os terpenoides voláteis também são metabólitos especializados e fornecem alguns resultados preliminares muito interessantes que indicam um possível uso dessas substâncias. Nesse caso, as cadeias produtivas existentes nas indústrias produtoras de óleos essenciais aumentam a sustentabilidade dessa exploração. Esses compostos podem ser encontrados em várias espécies de plantas com usos antigos, como alimentos, medicamentos e aromáticos, como erva-cidreira (*Melissa officinalis*), capim-limão (*Cymbopogon citratus*), alfazema (*Lavandula angustifolia*), gerânio (*Pelargonium graveolens*), manjericão (*Ocimum basilicum*), tangerina (*Citrus reshni*), canela (*Cinnamomum zeylanicum*), camomila (*Matricaria recutita*), gengibre (*Zingiber officinale*) e copaíba (*Copaifera* sp.) (SILVA *et al*, 2020).

Como inibidores de TMPRSS2, o acoplamento molecular para inibidores 3CLpro também indica que as algas são uma fonte potencial de metabólitos anti-COVID-19. Gentile *et al.* (2020) avaliou o acoplamento molecular em banco de dados de metabólitos de drogas marinhas como polifenóis de algas, conhecidos

como florotaninos, e derivados de quercetina. Esses compostos foram isolados de espécies do gênero *Sargassum* (GENTILE *et al*, 2020).

Os inibidores da RNA polimerase dependente de RNA (RdRp) são um mecanismo extremamente específico para inibir a replicação do vírus anti-SARS-CoV-2. Embora os inibidores da RNA polimerase sejam menos tóxicos do que os inibidores ECA 2 ou TMPRSS2, sua exploração aplicada ao tratamento com coronavírus é pouco, sugere-se apenas duas substâncias que inibem a tradução do RNA dos coronavírus, o remdesivir e um derivado sintético de 1,4-diazepano (HERMANN, 2017).

Nosso estudo visa sintetizar sistematicamente os dados disponíveis sobre o potencial terapêutico dessa classe de substâncias naturais para o tratamento da infecção por SARS-COV-2, por meio de uma ampla revisão de escopo.

2. JUSTIFICATIVA

Considerando-se da necessidade de explorar alternativas para controlar a propagação de infecções, com particular atenção ao seu modo de transmissão, e alívio de sintomas causados, muitas pesquisas têm sido realizadas sobre princípios ativos naturais como os flavonoides, amplamente distribuído na nossa dieta diária, em alimentos como cebola roxa, brócolis, chá preto, vinho tinto e frutas (principalmente maçã) e muito utilizado como fitoterápico. Pensando no fortalecimento do sistema imune, os flavonoides representam uma fonte de compostos antivirais, antimicrobianos e anti-inflamatório, os quais são fornecidos por plantas que têm impacto na saúde humana e favorecem uma economia em recursos por sua biodisponibilidade.

3. OBJETIVOS

Conduzir uma revisão de escopo de estudos que avaliaram substâncias da classe dos flavonoides como possível terapia complementar para COVID-19.

4. CAPÍTULO

Flavonoid as possible therapeutic targets against COVID-19: a scoping review

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

Methods: The PubMed and Scopus electronic databases were searched for studies that evaluated 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 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 key 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 highest number of targets 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 i*n vivo* assays to assist in the development of drugs for the treatment and/or prevention of COVID-19.

Keywords: Coronavirus; Medicinal Plants; Respiratory Syndrome; *In silico*, Bioactives.

1. 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 and side effects of this disease 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, including medicinal plants, are commonly used as models for the synthesis of new antiviral drugs due to their availability in the nature and variability of compounds with therapeutic potential. Around 50% of all approved drugs between 1981-2014 were derivative 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 in 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].

In silico methodology uses computational techniques of molecular modeling. It is one of the most used tools for the study and the development of new drugs or for the repositioning of old drugs [6 - 8]. Molecular modeling is defined as the investigation of the structures and molecular properties of the substances of interest, by means of computational chemistry and graphic visualization techniques. This allows building 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 SARS-CoV-2: 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).

Nonetheless, to date, no synthesized and updated evidence on the effects of flavonoids against SARS-CoV-2 has been found. Our study aims to systematically synthetize the available data on the therapeutic potential of this class of natural substances for treating this infection, as well as their mechanisms of action, by means of a broad scoping review.

2. 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 [14], Cochrane Handbook for Systematic Reviews of Interventions version 6.2, and Joanna Briggs Institute methodology for scoping reviews [15, 16]. This study was registered in the OSF (Open Science Framework), which can be found via the doi: 10.17605/OSF.IO/7QXV8.

The search was performed in MEDLINE/ PubMed and Scopus electronic databases, without limits for language or publication date. The main descriptors

were related to COVID-19 and flavonoids (see complete search strategy in appendix A provided in the supplemental material). Manual searches on the reference list of included studies were also conducted.

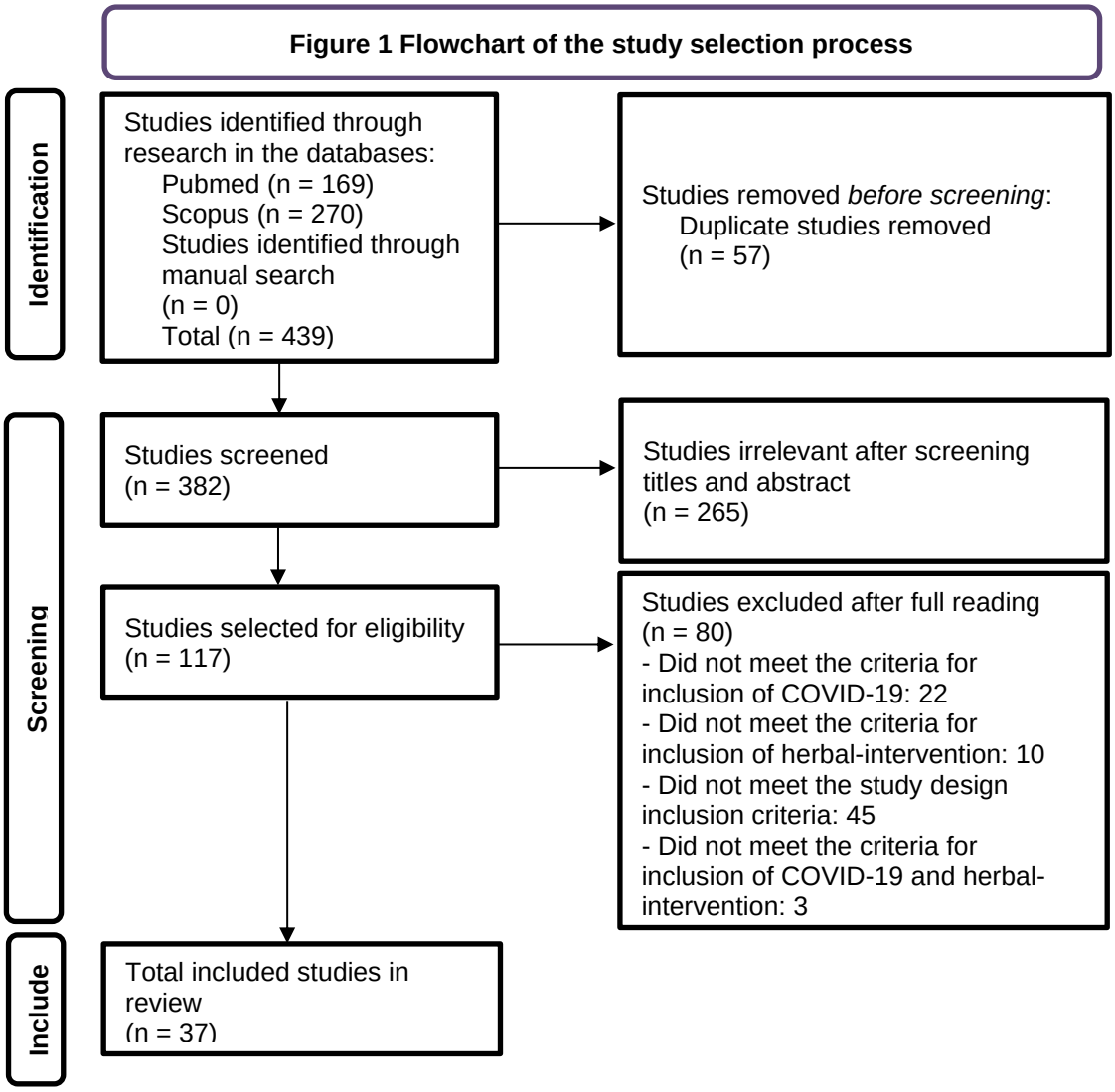
Was included *in silico* studies that evaluated the use of flavonoids (any type and in any dose/regimen), alone or combined with other substances, for the management of SARS-CoV-2 infections at any stage. During the screening phase (title and abstract) and full-text eligibility phase, articles were excluded if they were written in non-Roman characters, designed as case-reports, simple reviews, non-systematic, systematic reviews with or without meta-analysis, and if they analyzed synthetic or 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 and computer programs, and main effects/outcomes. These data were extracted from each article and were synthetically transformed into the table that is presented in this study.

All steps in the study selection and data extraction phases were performed by two authors independently, with a third author to resolve discrepancies during the consensus meetings.

3. RESULTS

The search strategy yielded 382 articles, after the exclusion of duplicates. During the screening process, 265 records were deemed irrelevant. From the 117 studies read in full, 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 (Figure 1).



Following in Table 1, shows the main characteristics of these 37 studies included. All of them 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 main computer programs used in this studies were 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.

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

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 [17]	United Kingdom	Neohesperidin, myricitin, quercetin, 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 [18]	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 [19]	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 [20]	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 [21]	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 [22]	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 [23]	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 [24]	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 [25]	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)

Wang et al., 2020 [26]	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 [27]	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 [28]	Egypt	Phacelianin, gentiodelphin, cyanidin 3-glucoside, cyanidin 3-rutinoside, pelargonidin 3-glucoside, delphinidin 3-aminoglucoside	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 [29]	Spain	Quercetin	AutoDock	3CLpro (6Y2E)	Quercetin showed the best binding energy (-7.50 kcal/mol).
Singh et al., 2020 [30]	India	EGCG (epigallocatechin-3-gallate), theaflavin (TF1), theaflavin-3'-*O*-gallate (TF2a), theaflavin-3'-gallate (TF2b), theaflavin-3,3'-	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).

		digallate (TF3), hesperidin, quercetagetin, and myricitin			
Pandey et al., 2020 [31]	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 [32]	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 [33]	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).
Maurya et al., 2020 [34]	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 [35]	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 [36]	Saudi Arabia	Quercetin	Maestro Package, AMBER	PLpro (6w9c)	Quercetin showed the best binding energy (-7.75 kcal/mol).
Alagu et al., 2021 [37]	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 [38]	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 [39]	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 [40]	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 [41]	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 [42]	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 [43]	India	Rutin, hesperidin, epigallocatechin gallate, epigallocatechin, myricitin, quercetin, glabridin, rhoifolin, vitexin	SwissDock server, Pymol	Mpro (6Y84)	Rutin presented the best binding energy (-9.55 kcal/mol).
Islam et al., 2020 [44]	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 [45]	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 [46]	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 [47]	India	Narcissoside	Software Molegro Virtual Docker (MVD), Pubchem	3CLpro (6W63)	Narcissoside showed the best binding energy (-180.74 kcal/mol).
Joshi et al., 2020 [48]	India	Quercetin, cryoseriol, 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 [49]	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 [50]	Egypt	Kaempferol	DMP, RCSB	Mpro (6LU7)	Kaempferol showed the best binding energy (-8.12 kcal/mol).
Glinsky, 2020 [51]	United States	Quercetin	Gene Expression Omnibus (GEO)	ACE II	There was no apply binding energy.
Gorla et al., 2021 [52]	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.

Studies on 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) [23, 27, 31, 34, 37, 42, 52].

Quercetin also presented effects on the inhibition of PLpro according to Fatoki et al. [33] and Kandeel et al. [36] (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) [23] and luteolin (binding energy of -6.80 kcal/mol) [42].

Among the flavonoids with 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 [21, 23, 24, 28, 33, 35, 42, 45 - 47]. Narcissoside has the highest binding energy (-180.74 kcal/mol) in this scenario [47]. On the other hand, epigallocatechin presented binding energy above -12.90 kcal/mol against RdRP [22]. Finally, the most promising flavonoids inhibiting 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 [22, 25, 31, 32, 34, 37, 38, 48, 52].

Three of the studies evaluated for data extraction (Glinsky [51], Ruan et al. [40] Wang et al. [26]) 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 values of binding energy occurred due to the different programs used in the articles since each program has a distinct algorithm and formula for calculating energy [53]. Despite the heterogeneity between the methodologies used, a ranking of the most promising flavonoids was suggested, classified according to the software used, lower binding energy, and number of targets (Table 2).

Table 2 Classification of energies, programs, and targets

Flavonoid	Binding energy	Target	Author and Year	Program
Amentoflavone	-8.49 kcal/mol	3CLpro	Chitranshi et al., 2020	AutoDock v4.2
Baicalein	-7.80 kcal/mol	3CLpro	Tao et al., 2020	AutoDock vina v1.1.2
Biochanin A	-78.41 kcal/mol	Protein Spike	Gorla et al., 2021	Molegro Virtual Docker v6.0
Calophyllolide	-9,30 kcal/mol	Mpro	Vijayakumar et al., 2020	AutoDock vina v1.1.2
Calophyllolide	-7.90 kcal/mol	Protein Spike	Vijayakumar et al., 2020	AutoDock vina v1.1.2
Calophyllolide	-8.70 kcal/mol	RdRP	Vijayakumar et al., 2020	AutoDock vina v1.1.2
Cyanidin	-8.20 kcal/mol	ACE II	Joshi et al., 2021	AutoDock vina*
Cyanidin 3-glucoside	-8.40 kcal/mol	Mpro	Islam et al., 2020	AutoDock vina*
Cyanidin 3-rutinoside	-17.02 kcal/mol	3CLpro	Khalifa et al., 2020	MOE (Molecular Operating Environment Software)*
Delphinidin-3,5-diglucoside	-13.60 kcal/mol	ACE II	Sharma and Shanavas, 2020	Glide package of Schrodinger chemical simulation software*
Delphinidin-3,5-diglucoside	-12.20 kcal/mol	Mpro	Sharma and Shanavas, 2020	Glide package of Schrodinger chemical simulation software*
Delphinidin-3-sambubioside-5-glucoside	-12.37 kcal/mol	Mpro	Fakhar et al., 2021	Package Schrodinger software suite (Maestro, version 11.6)
Epigallocatechin	-12.90 kcal/mol	RdRP	Joshi et al., 2021	AutoDock vina*
Eriodictyol	-9.90 kcal/mol.	Mpro	Joshi et al., 2021	AutoDock vina*
Eriodictyol	-7.90 kcal/mol	Protein Spike	Vijayakumar et al., 2020	AutoDock vina v1.1.2
Fisetin	-8.50 kcal/mol	Spike Protein	Pandey et al., 2020	AutoDock vina*
Hesperetin	-7.90 kcal/mol	Mpro	Narkhede et al., 2020	AutoDock vina v1.0
Hesperidin	-8.00 kcal/mol	3CLpro	Mahdian et al., 2020	AutoDock vina*
Hesperidin	-9.40 kcal/mol	PLpro	Mahdian et al., 2020	AutoDock vina*
Hesperidin	-7,40 kcal/mol	Protein Spike	Mahdian et al., 2020	AutoDock vina*
Hesperidin	-6.10 kcal/mol	TMPRSS2	Mahdian et al., 2020	AutoDock vina*
Kaempferol	-6.20 kcal/mol	Viral peptides	Hamza et al., 2021	AutoDock vina*
Luteolin	-5.37 kcal/mol	3 CLpro	Yu et al., 2020	AutoDock vina*

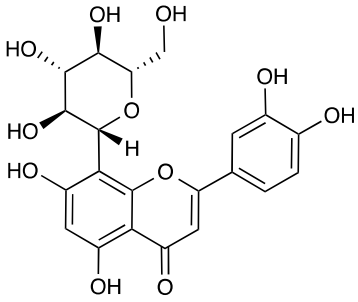
Luteolin	-6.80 kcal/mol	PLpro	Yu et al., 2020	AutoDock vina*
Luteolin	-7.00 kcal/mol	Protein Spike	Yu et al., 2020	AutoDock vina*
Luteolin	-7.80 kcal/mol	RdRP	Yu et al., 2020	AutoDock vina*
Luteolin	-9.80 kcal/mol	RdRP	Alamri et al., 2020	AutoDock vina v1.1.2
Narcissoside	-180.74 kcal/mol	3CLpro	Dubey and Dubey, 2020	Molegro Virtual Docker*
Naringin	-9.70 kcal/mol	3CLpro	Meyer-Almes, 2020	AutoDock vina*
Neohesperidin	-66.53 kcal/mol	TMPRSS2	Chikhale et al., 2020	Glide package of Schrodinger molecular modelling suite (Glide Score)*
Neohesperidin	-12.77 kcal/mol	TMPRSS2	Chikhale et al., 2020	Glide package of Schrodinger molecular modelling suite (Dock Score)*
Neohesperidin	-12.77 kcal/mol	TMPRSS2	Chikhale et al., 2020	Glide package of Schrodinger molecular modelling suite (Prime MM-GBSA)*
Orientin	-70.60 kcal/mol	ACE II	Alagu et al., 2021	AutoDock v4.2
Orientin	-90.20 kcal/mol	Mpro	Alagu et al., 2021	AutoDock v4.2
Orientin	-72.30 kcal/mol	Protein Spike	Alagu et al., 2021	AutoDock v4.2
Pectolinarin	-10.97 kcal/mol	3CLpro	Jo et al., 2020	Package Schrodinger software suite (Maestro, version 11.8.012)
Quercetin	-7.50 kcal/mol	3CLpro	Abian et al., 2020	AutoDock vina*
Quercetin	-8.20 kcal/mol	3Clpro	Fatoki et al., 2021	AutoDock vina v1.1.2
Quercetin	-11.30 kcal/mol	ACE II	Joshi et al., 2020	AutoDock vina*
Quercetin	-8.40 kcal/mol	ACE II	Tao et al., 2020	AutoDock vina v1.1.2
Quercetin	-4.41 kcal/mol	ACE II	Chikhale et al., 2020	AutoDock v4.2
Quercetin	-22.17 kcal/mol	ACE II	Pandey et al., 2020	AutoDock Raccoon
Quercetin	-92.05 kcal/mol	ACE II	Maurya et al., 2020	Molegro Virtual Docker v3.0.0
Quercetin	-9.90 kcal/mol	Mpro	Joshi et al., 2021	AutoDock vina*
Quercetin	-8.30 kcal/mol	Mpro	Joshi et al., 2020	AutoDock vina*
Quercetin	-10.20 kcal/mol	PLpro	Fatoki et al., 2021	AutoDock vina v1.1.2
Quercetin	-8.50 kcal/mol	Protein Spike	Pandey et al., 2020	AutoDock vina*
Quercetin	-86.22 kcal/mol	Protein Spike	Maurya et al., 2020	Molegro Virtual Docker v3.0.0
	-9.20 kcal/mol	RdRP	Fatoki et al., 2021	AutoDock vina v1.1.2

Rhamnetin	-8.20 kcal/mol	Mpro	Fischer et al., 2020	AutoDock vina v1.1.2
Rhoifolin	-9.56 kcal/mol	3CLpro	Jo et al., 2020	Package Schrodinger software suite (Maestro, version 11.8.012)
Rutin	-9.30 kcal/mol	Envelope protein	Bhowmik et al., 2020	AutoDock 4 and vina
Rutin	-9.55 kcal/mol	Mpro	Das et al., 2020	Swissdock*
Silymarin	-121.28 kcal/mol	ACE II	Gorla et al., 2021	Molegro Virtual Docker v6.0
Theaflavin-3,3'- digallate	-9.90 kcal/mol	RdRP	Singh et al., 2020	AutoDock vina v1.1.2

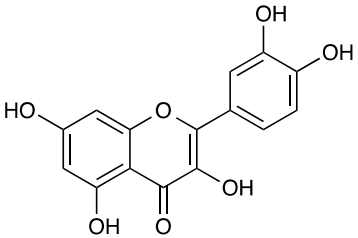
* Version not specified by the authors.

In Figure 2 below, shows the mains chemical structures of flavonoids numbered in sequence (1 to 8). 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.

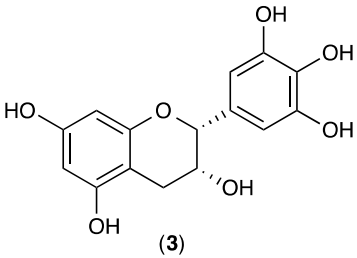
Moreover, with the versions of Molegro Virtual Docker software, narcissoside **(4)** showed the lowest energy (-180.74 kcal/mol). In this program, the most promising flavonoids are narcissoside **(4)**, with an energy of -180.74 kcal/mol and silymarin **(5)**, with an energy of -121.28 kcal/mol, both 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. (The chemical structures of the flavonoids mentioned are available in Figure 2, following the sequence of the software considered for classification).



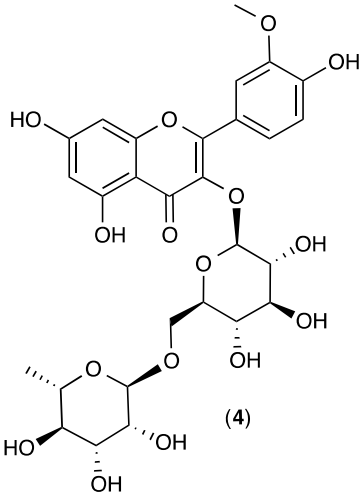
(**1**)



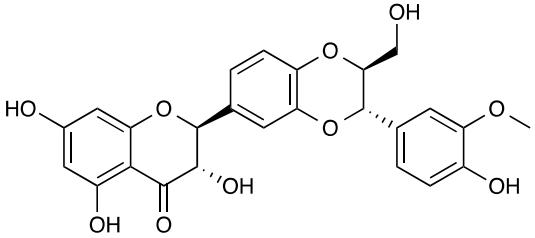
(**2**)



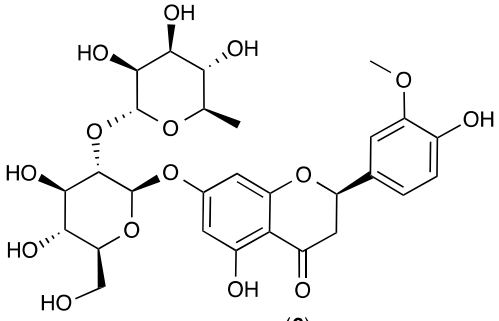
(**3**)



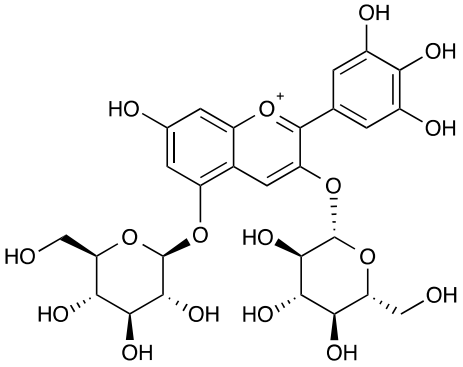
(**4**)



(**5**)



(**6**)



(**7**)

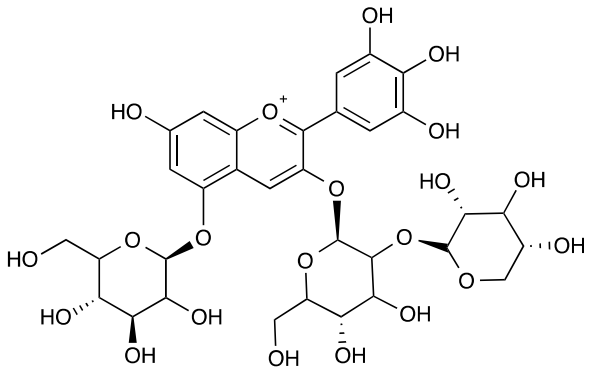


Figure 2 Chemical structures described in the most promising results of the 37 in silico studies

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.

4. DISCUSSION

This comprehensive scoping review has systematically synthesized the available evidence on the potential therapeutic effects of different flavonoids against SARS-CoV-2.

Was 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 by 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 [54, 55].

In this study, was present molecular docking, which is 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, predicting possible modes of action or lack thereof. Compounds with lower binding energy may have higher affinity for target proteins [56, 57].

Several studies, at the beginning of the pandemic, 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 inhibition of proteins such as Mpro or 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 [58 - 60].

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 [61, 62].

After the adoption and penetration stages, the denudation occurs, in wich 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) [63, 64].

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 transcription of subgenomic messenger Rs RNA used to encode viral structural proteins and transcribe new genomic RNA, originating new viruses [65].

Flavonoids are phenolic compounds that can be subdivided into different groups, including flavonols, flavones, flavanones, catechins, anthocyanins, isoflavones, dihydrophenols, and chalcones, which are compounds known to have antiviral activity, acting mainly on the viral DNA polymerase enzyme and for having hydroxyl groups that favor interactions with key residues. Additionally, the position and number of hydrogen bonds are important 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) [66].

Within the viral cycle, the SARS-CoV-2 replication mechanism was found to be primarily led by RdRP, a complex of non-structural proteins [67, 68].

Viral RNA is translated into various polyproteins by the action of the main protease (Mpro) on SARS-CoV-2. The human equivalent for this particular protease is absent, making this a safe target for anti-SARS-CoV-2 agents. In molecular modeling, the removal/mutation of the amino acids present 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 [69 - 71].

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

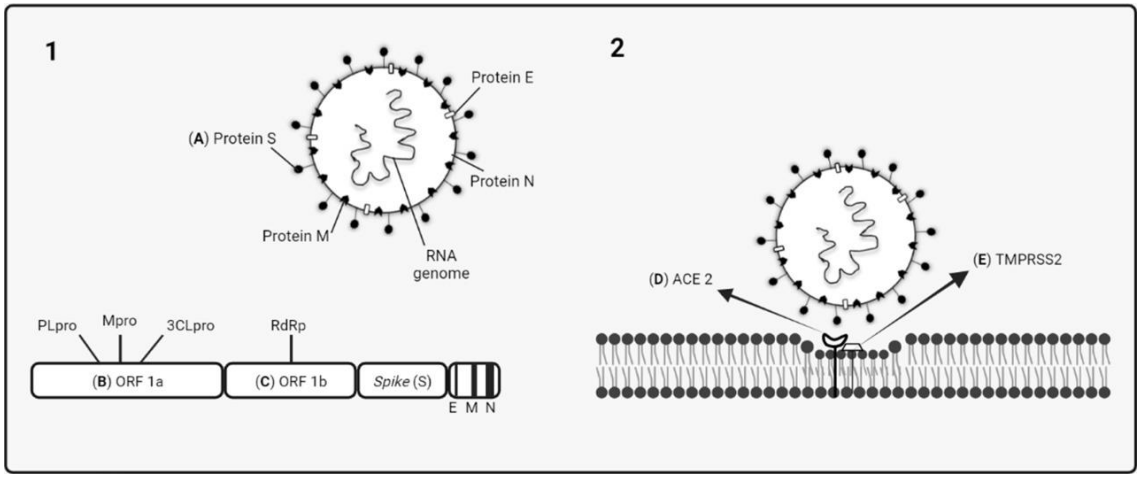


Figure 3 SARSCoV-2 life cycle in the main flavonoids discuss in the scoping review.

***1**. Shows the main structural and non-structural target proteins of SARS-CoV-2 discussed in the review. The promising flavonoids analyzed in silico study for (**A**) protein S were quercetin, eriodictyol, hesperidin, calophyllolide, fisetin, orientin, luteolin, and biochanin A; (**B**) PLpro were quercetin, eriodictyol, hesperidin, and luteolin; (**B**) Mpro were rutin, kaempferol, delphinidin-3-sambubioside-5-glucoside, quercetin, eriodictyol, calophyllolide, delphinidin-3,5-diglucoside, orientin, rhamnetin, and cyanidin-3-glucoside; (**B**) 3CLpro were amentoflavone, quercetin, hesperidin, naringin, pectolinarin, cyanidin-3-rutinoside, baicalein, luteolin, rhoifolin, and narcissoside; (**C**) 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. Fonte: o autor*

The search for new substances to treat a disease, and even a new disease, are based on the search for articles that present some confirmation of substances that promoted positive effects in similar diseases. Thus, this work shows researches 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, encouraging the research of these flavonoids for *in vitro* and *in vivo* studies.

Among all the flavonoids, compounds from the flavones' class were the firsts to be associated with antiviral properties. In the late 1940s, quercetin was described as having "prophylactic effect" against rabies virus in infected rats [72]. We found this compound with promising activity against SARS-CoV-2 (energies ranging from -4.41 to -92.05 kcal/mol). Previous studies show that 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.

[73] demonstrated a reduction in the virucide activities of some virus with the use of this substance, while Carvalho et al. [74] 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 [72, 75]. 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 [76], which may justify its antiviral effect, including against SARS-CoV-2. Myricitrin has recently been associated with activities against HIV, influenza, and leukemia [77]. 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 in the interaction between viral envelope proteins and CD4+ cells, thus reducing the virus binding capacity to the host cell [78, 79].

Orientin, a flavonoid from the *Trollius chinensis* Bunge (Ranunculaceae) flowers is currently used in the treatment of respiratory tract infections in Asian countries [80]. 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 [81].

Some anthocyanins previously demonstrated antioxidant and anti-inflammatory properties (e.g., inhibition of LDL oxidation) and with potential to decrease the risk of cardiovascular diseases and cancer [82 - 86]. Compounds such as phacelianin and cyanidin additionally have anti-mutagenic and antiviral activities [87 - 89].

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 related to these substances include hepatic protection, antitumor, and anti-inflammatory vascular effects [90,91].

Compounds such as gallocatechin and neohesperidin (dihydrochalcones class), have proved antioxidant activity similar to vitamin C and vitamin E. Thus, they can strength the immune system and help inhibiting the action of free radicals, especially on the cardiovascular system [92, 93].

Among the flavanones, hesperidin may play a significant role in the human system as anti-inflammatory, since it inhibits both the cyclooxygenase (COX) and lipoxygenase pathways [94, 95]. Its anti-inflammatory effects are additionally associated with the inhibition of the synthesis of prostaglandins (PGE2 and PGE2a) [96]. 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 cardioprotective [97].

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 [98], including in the central nervous system [99].

Computational molecular modeling precedes *in vitro* and *in vivo* studies, demonstrating that there are great possibilities of interaction through molecular docking between compounds and the molecular target [100].

In summary, all the studies used virtual molecular docking models to verify the affinity of compounds from the flavonoid class with key 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 highest number of 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 were possible since the heterogeneity between studies (e.g., study design and methods used/programs, type of flavonoid, outcome measure) is very high. The

focus of this review was on the antiviral effects of flavonoids. Thus, other natural compounds (alone or combined) may have some effect in this context and should be better evaluated in other studies.

5. CONCLUSION

In this scoping review, *in silico* studies models demonstrated that some flavonoids showed the lowest binding energies and most numbers for different targets of action (ranging from three to six - PLpro, Mpro, 3CLpro, spike protein, ACE2, TMPRSS2), like orientin, quercetin, epigallocatechin, narcissoside, silymarin, neohesperidin, delphinidin-3,5-diglucoside, and delphinidin-3-sambubioside-5-glucoside, and they show promising antiviral activities against SARS-CoV-2.

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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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5. CONSIDERAÇÕES FINAIS

Os fitoquímicos de ocorrência natural fornecem um recurso valioso e poderoso de compostos químicos que exibem propriedades antivirais. Modificações químicas dessas estruturas, guiadas por simulações de acoplamento baseadas em computador, também podem aumentar sua potência e/ ou seletividade. Esta revisão de escopo de estudos avaliou substâncias da classe dos flavonoides, que atuam fortalecendo o sistema imune, através de mecanismos com ações antivirais, além de favorecem uma economia em recursos por sua biodisponibilidade, mostrando que a exploração de alternativas para controlar a propagação de infecções, com particular atenção ao seu modo de transmissão, e alívio de sintomas causados, podem ser de conclusão favorável frente à metodologia *in silico* de estudos, contribuindo para o desenvolvimento de estudos *in vivo* e *in vitro* sobre a ação desses compostos.

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7. APÊNDICES

Supplementary material

Flavonoid as possible therapeutic targets against COVID-19: a scoping review

Appendix A. Complete search strategies

Data base	Search strategy
MEDLINE/ PUBMED (n = 169) September, 2020	flavonoids[TIAB] OR bioflavonoids[TIAB] OR anthocyanins[TIAB] OR cyanidin[TIAB] OR delphinidin[TIAB] OR malvidin[TIAB] OR pelargonidin[TIAB] OR peonidin[TIAB] OR petunidin[TIAB] OR aurone[TIAB] OR aureusin[TIAB] OR aureusidin[TIAB] OR cernuoside[TIAB] OR leptosin[TIAB] OR maritimein[TIAB] OR maritimetin[TIAB] OR sulfurein[TIAB] OR sulfuretin[TIAB] OR benzoflavones[TIAB] OR beta-naphthoflavone[TIAB] OR biflavonoids[TIAB] OR hinoquiflavona[TIAB] OR chalcones[TIAB] OR butein[TIAB] OR coreopsin[TIAB] OR flavocavin-B[TIAB] OR isoalipurposide[TIAB] OR isoliquiritigenin[TIAB] OR isoliquiritin[TIAB] OR marein[TIAB] OR ocanin[TIAB] OR dihydroflavonoid[TIAB] OR alpinon[TIAB] OR ampelopsin[TIAB] OR dihydromyrecetin[TIAB] OR aromadendrin[TIAB] OR aromodedrin[TIAB] OR dihydrokaempferol[TIAB] OR astilbin[TIAB] OR dihidromorin[TIAB] OR garbanzol[TIAB] OR lecontin[TIAB] OR pinobanksin[TIAB] OR strobobanksin[TIAB] OR taxifolin[TIAB] OR dihydroquercetin[TIAB] OR dihydrochalcone asebogenin[TIAB] OR asebotin[TIAB] OR davidigenin[TIAB] OR davidioside[TIAB] OR phloretin[TIAB] OR phloridzin[TIAB] OR uvangoletin[TIAB] OR flavanones[TIAB] OR alpinetin[TIAB] OR butin[TIAB] OR citromitin[TIAB] OR eriodictyol[TIAB] OR farrerol[TIAB] OR glabranin[TIAB] OR hesperetin[TIAB] OR hesperidin[TIAB] OR liquiritigenin[TIAB] OR naringenin[TIAB] OR naringin[TIAB] OR plantagoside[TIAB] OR pinocembrin[TIAB] OR pinostrobin[TIAB] OR prunin[TIAB] OR sakuranetin[TIAB] OR flavanols[TIAB] OR catechin[TIAB] OR epicatechin[TIAB] OR gallocatechin[TIAB] OR epigallocatechin[TIAB] OR flavones[TIAB] OR acacetin[TIAB] OR apiin[TIAB] OR apigenin[TIAB] OR baohuoside-1[TIAB] OR chrysin[TIAB] OR chrysoeriol[TIAB] OR diosmin[TIAB] OR escutellarein[TIAB] OR flavoxate[TIAB] OR luteolin[TIAB] OR narcissoside[TIAB] OR schaftoside[TIAB] OR tricetin[TIAB] OR tricin[TIAB] OR flavonolignans[TIAB] OR silymarin[TIAB] OR flavonols[TIAB] OR astragalin[TIAB] OR centaureidin[TIAB] OR kaempferols[TIAB] OR fisetin[TIAB] OR galangin[TIAB] OR gossypetin[TIAB] OR herbacetin[TIAB] OR isorhamnetin[TIAB] OR myricetin[TIAB] OR myricitrin[TIAB] OR morin[TIAB] OR patuletin[TIAB] OR quercetin[TIAB] OR rutin[TIAB] OR “flavonoids C-heterosides”[TIAB] OR lucenin-2[TIAB] OR orientin[TIAB] OR schaftoside[TIAB] OR escoparin[TIAB] OR vicenin-1[TIAB] OR vicenin-2[TIAB] OR vicenin-3[TIAB] OR violantin[TIAB] OR vitexin[TIAB] OR isoflavonoids[TIAB] OR pterocarpan[TIAB] OR cumestan[TIAB] OR isoflavone[TIAB] OR biochanin-A[TIAB] OR

	daidzein[TIAB] OR formononetin[TIAB] OR genistein[TIAB] OR genistin[TIAB] OR malonilononin[TIAB] OR ononin[TIAB] OR rotenoid[TIAB] OR rotenone[TIAB] OR isoflavanone[TIAB] OR dalbergiodin[TIAB] OR dihydroonon[TIAB] OR dihydroxiformononetin[TIAB] OR pterocarpan[TIAB] OR medicarpin[TIAB] OR soforajaponicina[TIAB] OR isoflavan[TIAB] OR equol[TIAB] OR vestitol[TIAB] OR sativan[TIAB] OR coumestan[TIAB] OR coumestrol[TIAB] OR neoflavonoid[TIAB] OR phloretin[TIAB] OR "polyphloretin phosphate"[TIAB] OR proanthocyanidins[TIAB] OR leucoanthocyanidins[TIAB] AND (Coronavirus[TIAB] OR SARS[TIAB] OR "Severe acute respiratory syndrome" [TIAB] OR MERS[TIAB] OR "Middle East Respiratory Syndrome" [TIAB] OR SARS-CoV-2[TIAB] OR COVID-19[TIAB] OR 2019-nCoV[TIAB] OR Coronavirus[MH] OR "SARS Virus" [MH] OR "Coronavirus Infections" [MH] OR "Severe Acute Respiratory Syndrome"[MH] OR "Middle East Respiratory Syndrome Coronavirus" [MH])
SCOPUS (n = 270) September, 2020	flavonoids OR bioflavonoids OR anthocyanins OR cyanidin OR delphinidin OR malvidin OR pelargonidin OR peonidin OR petunidin OR aurone OR aureusin OR aureusidin OR cernuoside OR leptosin OR maritimein OR maritimetin OR sulfurein OR sulfuretin OR benzoflavones OR beta-naphthoflavone OR biflavonoids OR hinoquiflavona OR chalcones OR butein OR coreopsin OR flavocavin-B OR isoalipurposide OR isoliquiritigenin OR isoliquiritin OR marein OR ocanin OR dihydroflavonoid OR alpinon OR ampelopsin OR dihydromyrecetin OR aromadendrin OR aromodedrin OR dihydrokaempferol OR astilbin OR dihidromorin OR garbanzol OR lecontin OR pinobanksin OR strobobanksin OR taxifolin OR dihydroquercetin OR dihydrochalcone asebogenin OR asebotin OR davidigenin OR davidioside OR phloretin OR phloridzin OR uvangoletin OR flavanones OR alpinetin OR butin OR citromitin OR eriodictyol OR farrerol OR glabranin OR hesperetin OR hesperidin OR liquiritigenin OR naringenin OR naringin OR plantagoside OR pinocembrin OR pinostrobin OR prunin OR sakuranetin OR flavanols OR catechin OR epicatechin OR gallocatechin OR epigallocatechin OR flavones OR acacetin OR apiin OR apigenin OR baohuoside-1 OR chrysin OR chrysoeriol OR diosmin OR escutellarein OR flavoxate OR luteolin OR narcissoside OR schaftoside OR tricetin OR tricin OR flavonolignans OR silymarin OR flavonols OR astragalin OR centaureidin OR kaempferols OR fisetin OR galangin OR gossypetin OR herbacetin OR isorhamnetin OR myricetin OR myricitrin OR morin OR patuletin OR quercetin OR rutin OR "flavonoids C-heterosides" OR lucenin-2 OR orientin OR schaftoside OR escoparin OR vicenin-1 OR vicenin-2 OR vicenin-3 OR violantin OR vitexin OR isoflavonoids OR pterocarpan OR cumestan OR isoflavone OR biochanin-A OR daidzein OR formononetin OR genistein OR genistin OR malonilononin OR ononin OR rotenoid OR rotenone OR isoflavanone OR dalbergiodin OR dihydroonon OR dihydroxiformononetin OR pterocarpan OR medicarpin OR soforajaponicina OR isoflavan OR equol OR vestitol OR sativan OR coumestan OR coumestrol OR neoflavonoid OR phloretin OR "polyphloretin phosphate" OR proanthocyanidins OR leucoanthocyanidins AND

	Coronavirus OR SARS OR “Severe acute respiratory syndrome” OR MERS OR “Middle East Respiratory Syndrome” OR SARS-CoV-2 OR COVID-19 OR 2019-nCoV OR Coronavirus OR “SARS Virus” OR “Coronavirus Infections” OR “Severe Acute Respiratory Syndrome” OR “Middle East Respiratory Syndrome Coronavirus”

Appendix B - List of inclusion and exclusion criteria for studies

Design:

Included: *in silico.*

Excluded: those not original articles designed as case-reports, simple reviews, non-systematic, systematic reviews with or without meta-analysis and synthetic and semi-synthetic flavonoids.

Non-COVID-19:

Included: studies performed with SARS-CoV-2.

Excluded: studies that nowhere in the text made it clear that SARS-CoV-2 was analyzed.

Language:

Included: studies written in Ibero-romance language or english.

Excluded: any studies that do not correspond to the above languages (non-Roman characters).

Non-herbal intervention:

Included: studies that used isolated or associated flavonoids (flavonoid plus another substance, compound or medicine).

Excluded: studies that argued the use of compounds other than the flavonoid class and/or that evaluated crude extract and/or fractions of plants rich in flavonoids and/or studies that used compounds whose name was not specified or protected by drug/ chemical patent.

Appendix C. Studies excluded after full reading

	Study (Authors, year)	Title	Reason for exclusion
1	Abbas *et al* (2019)	The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2)	Article not related to the covid theme
2	AbdelMassih *et al* (2020)	A multicenter consensus: A role of furin in the endothelial tropism in obese patients with COVID-19 infection	Article not related to the covid and flavonoide theme
3	Abe T (1999)	Infantile leukemia and soybeans--a hypothesis	Article not related to the covid theme
4	Abu Bakar *et al* (2018)	Design, Synthesis and Docking Studies of Flavokawain B Type Chalcones and Their Cytotoxic Effects on MCF-7 and MDA-MB-231 Cell Lines	Article not related to the covid theme
5	Adithya *et al* (2020)	The Plausible role of Indian Traditional Medicine in combating Corona Virus (SARS-CoV 2): a mini-review	Article not original by design
6	Ahmed *et al* (2003)	Synthesis and antihepatotoxic activity of some heterocyclic compounds containing the 1,4-dioxane ring system	Article not related to the covid theme
7	Ahmed *et al* (2005)	Isolation, antihypertensive activity and structure activity relationship of flavonoids from three medicinal plants	Article not related to the covid theme
8	Ahmed *et al* (2016)	Flavonoids of Calligonum polygonoides and their cytotoxicity	Article not related to the covid theme
9	Ahmed *et al* (2018)	Methylation and acetylation enhanced the antidiabetic activity of some selected flavonoids: In vitro, molecular modelling and structure activity relationship-based study	Article not related to the covid theme
10	Akher *et al* (2019)	Discovery of novel natural flavonoids as potent antiviral candidates against hepatitis C virus NS5B polymerase	Article not related to the covid theme
11	Alam e Khan (2019)	3D-QSAR, Docking, ADME/Tox studies on Flavone analogs reveal anticancer activity through Tankyrase inhibition	Article not related to the covid theme
12	Alves *et al* (2013)	Antimicrobial activity of phenolic compounds identified in wild mushrooms, SAR analysis and docking studies	Article not related to the covid theme
13	Amber *et al* (2017)	A review on antiviral activity of the Himalayan medicinal plants traditionally used to treat bronchitis and related symptoms	Article not original by design
14	Amić *et al* (2007)	SAR and QSAR of the antioxidant activity of flavonoids	Article not related to the covid theme
15	Amrutha *et al* (2014)	Discovery of lesser known flavones as inhibitors of NF-κB signaling in MDA-MB-231 breast cancer cells - A SAR study	Article not related to the covid theme
16	Anizon *et al* (2010)	Fighting tumor cell survival: Advances in the design and evaluation of Pim inhibitors	Article not related to covid and flavonoid theme
17	Arai *et al* (2015)	Structure-activity relationship of flavonoids as potent inhibitors of carbonyl reductase 1 (CBR1)	Article not related to the covid theme
18	Arioka *et al* (2010)	Potent inhibitor scaffold against Trypanosoma cruzi trans-sialidase	Article not related to the covid theme

19	Arshad *et al* (2020)	Coronavirus Disease (COVID-19) and Immunity Booster Green Foods: A Mini Review	Article not original by design
20	Artico *et al* (1998)	Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-1 integrase: synthesis, biological evaluation, and molecular modeling	Article not related to covid and flavonoid theme
21	Arts *et al* (2003)	A critical appraisal of the use of the antioxidant capacity (TEAC) assay in defining optimal antioxidant structures	Article not related to the covid theme
22	Arts *et al* (2004)	Antioxidant capacity of reaction products limits the applicability of the Trolox Equivalent Antioxidant Capacity (TEAC) assay	Article not related to the covid theme
23	Atrahimovich *et al* (2013)	The effects and mechanism of flavonoid-rePON1 interactions. Structure-activity relationship study	Article not related to the covid theme
24	Attar *et al* (2011)	Ferrocenyl chalcones versus organic chalcones: a comparative study of their nematocidal activity	Article not related to the covid theme
25	Attiq *et al* (2018)	Raging the war against inflammation with natural products	Article not related to covid and flavonoid theme
26	Aucoin *et al* (2020)	The effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review	Article not original by design
27	Babu *et al* (2013)	Experimental and theoretical advances in functional understanding of flavonoids as anti-tumor agents	Article not related to the covid theme
28	Bachevski *et al* (2020)	Back to the basics: Propolis and COVID-19	Article not related to the flavonoid theme
29	Badria *et al* (2005)	In vitro study of flavonoids, fatty acids, and steroids on proliferation of rat hepatic stellate cells	Article not related to covid and flavonoid theme
30	Bahrin *et al* (2016)	Antibacterial structure-activity relationship studies of several tricyclic sulfur-containing flavonoids	Article not related to the covid theme
31	Balachandar *et al* (2020)	COVID-19: Emerging protective measures	Article not related to the flavonoid theme
32	Balmeh *et al* (2020)	Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors	Article not related to the flavonoid theme
33	Bano *et al* (2020)	Nematicidal activity of flavonoids with structure activity relationship (SAR) studies against root knot nematode Meloidogyne incognita	Article not related to the covid theme
34	Bellavite e Donzelli *et al* (2020)	Hesperidin and SARS-CoV-2: New Light on the Healthy Function of Citrus Fruits	Article not original by design
35	Betti *et al* (2004)	Design, synthesis, and α1-adrenoceptor binding properties of new arylpiperazine derivatives bearing a flavone nucleus as the terminal heterocyclic molecular portion	Article not related to covid and flavonoid theme
36	Bhardwaj *et al* (2019)	Phytochemical Screening and Antioxidant Activity Study of Methanol Extract of Stems and Roots of Codonopsis clematidea from Trans-himalayan Region	Article not related to the covid theme

37	Bhuiyan *et al* (2017)	Quercetin inhibits advanced glycation end product formation via chelating metal ions, trapping methylglyoxal, and trapping reactive oxygen species	Article not related to the covid theme
38	Blasi *et al* (2011)	Drug discovery targeted at transthyretin cardiac amyloidosis: Rational design, synthesis, and biological activity of new transthyretin amyloid inhibitors	Article not related to covid and flavonoid theme
39	Botta *et al* (2005)	Prenylated flavonoids: Pharmacology and biotechnology	Article not related to the covid theme
40	Boumendjel A (2003)	Aurones: A subclass of flavones with promising biological potential	Article not original by design
41	Boumendjel *et al* (2002)	Recent advances in the discovery of flavonoids and analogs with high-affinity binding to P-glycoprotein responsible for cancer cell multidrug resistance	Article not related to the covid theme
42	Boumendjel *et al* (2005)	Anticancer multidrug resistance mediated by MRP1: Recent advances in the discovery of reversal agents	Article not related to the covid theme
43	Bullock *et al* (2005)	Structural basis of inhibitor specificity of the human protooncogene proviral insertion site in moloney murine leukemia virus (PIM-1) kinase	Article not related to covid and flavonoid theme
44	Butkovic *et al* (2004)	Kinetic Study of Flavonoid Reactions with Stable Radicals	Article not related to the covid theme
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48	Chan *et al* (2009)	Flavonoid dimers as bivalent modulators for P-glycoprotein-based multidrug resistance: Structure-activity relationships	Article not related to the covid theme
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50	Chang *et al* (2007)	Effects of flavonoids with different structures on proliferation of leukemia cell line HL-60	Article not related to the covid theme
51	Chen *et al* (2005)	Inhibition of SARS-CoV 3C-like Protease Activity by Theaflavin-3,3'-digallate (TF3)	Article not related to the covid theme
52	Chen *et al* (2011)	Houttuynia cordata blocks HSV infection through inhibition of NF-κB activation	Article not related to the covid theme
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59	Chledzik *et al* (2018)	Pharmacological Effects of Scutellarin, An Active Component of Genus Scutellaria and Erigeron: A Systematic Review	Article not related to the covid theme
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61	Choi *et al* (2004)	Reversal of P-glycoprotein-mediated MDR by 5,7,3′,4 ′,5′-pentamethoxyflavone and SAR	Article not related to the covid theme
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64	Chojnacka *et al* (2020)	Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus	Article not original by design
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67	Colunga *et al* (2020)	Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)	Article not original by design
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71	Coulerie *et al* (2012)	Biflavonoids of Dacrydium balansae with potent inhibitory activity on dengue 2 NS5 polymerase	Article not related to the covid theme
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80	Das *et al* (2020)	In-Silico approach for identification of effective and stable inhibitors for COVID-19 main protease (M(pro)) from flavonoid based phytochemical constituents of Calendula officinalis	Article not related to the flavonoid theme
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112	Gao *et al* (2004)	Structure-activity relationships for α-glucosidase inhibition of baicalein, 5,6,7-trihydroxyflavone: The effect of A-ring substitution	Article not related to the covid theme
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122	Guinobert *et al (*2018)	In vitro virucidal activity of an extract of cypress on human and bovine viruses	Article not related to the covid theme
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129	Heřmánková *et al* (2019)	Redox properties of individual quercetin moieties	Article not related to the covid theme
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134	Huang *et al* (2020)	Review on the potential action mechanisms of Chinese medicines in treating Coronavirus Disease 2019 (COVID-19)	Article not original by design
135	Ismayati *et al* (2018)	Utilization of Bark Condensed Tannin as Natural Preservatives Against Subterranean Termite. IOP Conference Series: Earth and Environmental Science; 2018.	Article not related to covid and flavonoid theme
136	Jeng *et al* (2009)	Membrane estrogen receptor-alpha-mediated nongenomic actions of phytoestrogens in GH3/B6/F10 pituitary tumor cells	Article not related to covid and flavonoid theme
137	Jeong *et al* (2009)	Neuraminidase inhibitory activities of flavonols isolated from Rhodiola rosea roots and their in vitro anti-influenza viral activities	Article not related to the covid theme
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156	Kuzuhara *et al* (2006)	DNA and RNA as new binding targets of green tea catechins	Article not related to the covid theme
157	Kuzuhara *et al* (2007)	Synergistic effects of multiple treatments, and both DNA and RNA direct bindings on, green tea catechins	Article not related to the covid theme
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161	Landis-Piwowar *et al* (2007)	Methylation suppresses the proteasome-inhibitory function of green tea polyphenols	Article not related to the covid theme
162	Landolt *et al* (1995)	Determination of structure-activity relationships of Annonaceous acetogenins by inhibition of oxygen uptake in rat liver mitochondria	Article not related to covid and flavonoid theme
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165	Lawson *et al* (2003)	A short method for the synthesis of 4,6-dimethoxy-1-azaaurones	Article not related to the covid theme
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179	Liang *et al* (2015)	(+)-Catechin inhibition of transmissible gastroenteritis coronavirus in swine testicular cells is involved its antioxidation	Article not related to the covid theme
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182	Lin *et al* (2005)	Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds	Article not related to the covid theme
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199	Martínez-Pérez *et al* (2016)	Antitumour activity of the novel flavonoid Oncamex in preclinical breast cancer models	Article not related to the covid theme
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204	Mercader & Pomilio (2012)	2D- and 3D-qsar studies of flavonoids, biflavones and chalcones: Antiviral, antibacterial, antifungal, and antimycobacterial activities	Article not related to the covid theme
205	Messina *et al* (2020)	Functional role of dietary intervention to improve the outcome of COVID-19: A hypothesis of work	Article not related to the flavonoid theme
206	Mhatre *et al* (2020)	Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review	Article not original by design
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208	Mitsuhashi *et al* (2008)	Pyrogallol structure in polyphenols is involved in apoptosis-induction on HEK293T and K562 cells	Article not related to the covid theme
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210	Morimoto & Komai (2006)	Insect antifeedant activity of natural products and the structure-activity relationship of their derivatives.	Article not related to the covid theme
211	Morimoto *et al* (2003)	Insect antifeedant activity of flavones and chromones against Spodoptera litura	Article not related to the covid theme
212	Mukne *et al* (2011)	Structure pre-requisites for isoflavones as effective antibacterial agents	Article not related to the covid theme
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214	Nachtergael *et al* (2013)	Measurement of translesion synthesis by fluorescent capillary electrophoresis: 7,8-Dihydro-8-oxodeoxyguanosine bypass modulation by natural products	Article not related to covid and flavonoid theme
215	Naeem *et al* (2020)	Herbs, Immunity and nCOVID-19: Old performers in new Pandemic	Article not original by design
216	Nagar *et al* (2008)	Pharmacophore mapping of flavone derivatives for aromatase inhibition	Article not related to the covid theme
217	Nain *et al* (2020)	Pathogenetic profiling of COVID-19 and SARS-like viruses	Article not original by design
218	Nazeam *et al* (2020)	Based on Principles and Insights of COVID-19 Epidemiology, Genome Sequencing, and Pathogenesis: Retrospective Analysis of Sinigrin and Prolixin(RX) (Fluphenazine) Provides Off-Label Drug Candidates	Article not original by design
219	Nenadis *et al* (2004)	Estimation of scavenging activity of phenolic compounds using the ABTS(*+) assay	Article not related to covid and flavonoid theme
220	Neugart *et al* (2016)	Influence of light and temperature on gene expression leading to accumulation of specific flavonol glycosides and hydroxycinnamic acid derivatives in kale (Brassica oleracea var. sabellica)	Article not related to the covid theme
221	Nguyen *et al* (2012)	Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris	Article not related to the covid theme

222	Ngwa *et al* (2020)	Potential of Flavonoid-Inspired Phytomedicines against COVID-19	Article not related to the flavonoide theme
223	Ni *et al* (2020)	Identification of Structural Features for the Inhibition of OAT3-Mediated Uptake of Enalaprilat by Selected Drugs and Flavonoids	Article not related to the covid theme
224	Nikhat & Fazil (2020)	Overview of Covid-19; its prevention and management in the light of Unani medicine	Article not original by design
225	Ofir *et al* (2003)	Inhibition of serotonin re-uptake by licorice constituents	Article not related to the covid theme
226	Ohmori *et al* (2011)	Integrated synthetic strategy for higher catechin oligomers	Article not related to the covid theme
227	Omosa *et al* (2014)	Antimicrobial flavonoids and diterpenoids from Dodonaea angustifolia	Article not related to the covid theme
228	Pabuprapap *et al* (2019)	Quercetin analogs with high fetal hemoglobin-inducing activity	Article not related to the covid theme
229	Pal & Saha (2014)	A review on structure-affinity relationship of dietary flavonoids with serum albumins	Article not related to the covid theme
230	Pan *et al* (2017)	Synthesis and anti-oxidant activity evaluation of (±)-Anastatins A, B and their analogs	Article not related to the covid theme
231	Pandey e Verma (2020)	An in-silico evaluation of dietary components for structural inhibition of SARS-Cov-2 main protease	Article not related to the flavonoid theme
232	Pandurangan *et al* (2019)	Synthesis, bioactivities and in-silico docking studies of azaleatin-a quercetin partial methyl ether: Sar study	Article not related to the covid theme
233	Park & Chiou (2004)	Structure-Activity Relationship (SAR) between Some Natural Flavonoids and Ocular Blood Flow in the Rabbit	Article not related to covid and flavonoid theme
234	Park *et al* (2012)	Synthesis and antiviral evaluation of 7-O-arylmethylquercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV)	Article not related to the covid theme
235	Park *et al* (2016)	Chalcones isolated from Angelica keiskei inhibit cysteine proteases of SARS-CoV	Article not related to the covid theme
236	Park *et al* (2017)	Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors	Article not related to the covid theme
237	Patil *et al* (2019)	Exploration of (hetero)aryl Derived Thienylchalcones for Antiviral and Anticancer Activities	Article not related to the covid theme
238	Paul *et al* (2019)	Interactions between a Bioflavonoid and c-MYC Promoter G-Quadruplex DNA: Ensemble and Single-Molecule Investigations	Article not related to the covid theme
239	Pérez-Garrido *et al* (2012)	Topological sub-structural molecular design approach: Radical scavenging activity	Article not related to covid and flavonoid theme
240	Ponce *et al* (2000)	Study of the Action of Flavonoids on Xanthine-Oxidase by Molecular Topology	Article not related to the covid theme
241	Potipiranun *et al* (2018)	Identification of Pinocembrin as an Anti-Glycation Agent and α-Glucosidase Inhibitor from Fingerroot (Boesenbergia rotunda): The tentative structure–activity relationship towards Mg-trapping activity	Article not related to the covid theme

242	Praud *et al* (2018)	Proanthocyanidins and the risk of prostate cancer in Italy	Article not related to the covid theme
243	Promden *et al* (2014)	Structure and antioxidant activity relationships of isoflavonoids from Dalbergia parviflora	Article not related to the covid theme
244	Protopopov *et al* (2020)	Flavone inspired discovery of benzylidenebenzofuran-3(2H)-ones (aurones) as potent inhibitors of human protein kinase CK2	Article not related to the covid theme
245	Putz *et al* (2009)	Quantum-SAR extension of the spectral-SAR algorithm. application to polyphenolic anticancer bioactivity	Article not related to the covid theme
246	Putz *et al* (2012)	From SPECTRAL-SAR to QUANTUM-SAR algorithm: Designing the polyphenolic anticancer bioactivity.	Article not related to the covid theme
247	Raghav & Garg (2014)	SAR studies of o-hydroxychalcones and their cyclized analogs and study them as novel inhibitors of cathepsin B and cathepsin H	Article not related to the covid theme
248	Ramesh *et al* (2020)	Indole chalcones: Design, synthesis, in vitro and in silico evaluation against Mycobacterium tuberculosis	Article not related to the covid theme
249	Rasouli & Jahanian (2015)	Improved performance and immunological responses as the result of dietary genistein supplementation of broiler chicks	Article not related to the covid theme
250	Rehakova *et al* (2014)	Evaluation of the antioxidant activity of several naturally occurring coumarins and their synthesized analogues by "ferric reducing antioxidant power" assay	Article not related to covid and flavonoid theme
251	Ren *et al* (2015)	Discovery of novel AHLs as potent antiproliferative agents	Article not related to the covid theme
252	Rosenkranz & Thampatty (2002)	SAR: Flavonoids and COX-2 Inhibition	Article not related to the covid theme
253	Roh C (2012)	A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide	Article not related to the covid theme
254	Rossi *et al* (2010)	Flavonoids, proanthocyanidins, and cancer risk: a network of case-control studies from Italy	Article not related to the covid theme
255	Rossi *et al* (2010)	Proanthocyanidins and the risk of colorectal cancer in Italy	Article not related to the covid theme
256	Rossi *et al* (2010)	Flavonoids, proanthocyanidins, and the risk of stomach cancer	Article not related to the covid theme
257	Rossi *et al* (2012)	Proanthocyanidins and other flavonoids in relation to pancreatic cancer: a case-control study in Italy	Article not related to the covid theme
258	Rossi *et al* (2013)	Proanthocyanidins and other flavonoids in relation to endometrial cancer risk: a case-control study in Italy	Article not related to the covid theme
259	Rouane *et al* (2018)	Qualitative and quantitative structure-activity relationships studies of quercetin derivatives as chemotherapeutic activity	Article not related to the covid theme
260	Russo *et al* (2020)	Roles of flavonoids against coronavirus infection	Article not original by design
261	Ryu *et al* (2010)	Biflavonoids from Torreya nucifera displaying SARS-CoV 3CL(pro) inhibition	Article not related to the covid theme
262	Sadeghipour *et al* (2005)	Flavonoids and tyrosine nitration: Structure-activity relationship correlation with enthalpy of formation	Article not related to the covid theme

263	Sadgrove *et al* (2020)	Antimicrobial isoflavones and derivatives from erythrina (Fabaceae): Structure activity perspective (SAR & QSAR) on experimental and mined values against staphylococcus aureus	Article not related to the covid theme
264	Saito & Nakajima (2005)	Stereoselective synthesis of procyanidin oligomers and their bioactivity	Article not related to the covid theme
265	Saito & Nakajima (2010)	Structure-activity relationships of synthesized procyanidin oligomers: DPPH radical scavenging activity and maillard reaction inhibitory activity	Article not related to the covid theme
266	Saito (2017)	Challenges and complexity of functionality evaluation of flavan-3-ol derivatives	Article not related to the covid theme
267	Santi *et al* (2019)	In vitro biological evaluation and molecular docking studies of natural and semisynthetic flavones from Gardenia oudiepe (Rubiaceae) as tyrosinase inhibitors	Article not related to the covid theme
268	Sanver *et al* (2016)	Experimental Modeling of Flavonoid-Biomembrane Interactions	Article not related to the covid theme
269	Sargiacomo *et al* (2020)	COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection?	Article not original by design
270	Sarwar *et al* (2018)	Structure activity relationship (SAR) and quantitative structure activity relationship (QSAR) studies showed plant flavonoids as potential inhibitors of dengue NS2B-NS3 protease	Article not related to the covid theme
271	Satsu *et al* (2018)	Suppressive effect of nobiletin and epicatechin gallate on fructose uptake in human intestinal epithelial Caco-2 cells	Article not related to the covid theme
272	Savi *et al* (2010)	Evaluation of antirotavirus activity of flavonoids	Article not related to the covid theme
273	Schneiderová & Šmejkal (2015)	Phytochemical profile of Paulownia tomentosa (Thunb). Steud	Article not related to the covid theme
274	Schwarz *et al* (2014)	Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus	Article not related to the covid theme
275	Scotti *et al* (2012)	SAR, QSAR and docking of anticancer flavonoids and variants: A review	Article not related to the covid theme
276	Seeram & Nair (2002)	Inhibition of lipid peroxidation and structure-activity-related studies of the dietary constituents anthocyanins, anthocyanidins, and catechins	Article not related to the covid theme
277	Seo *et al* (2016)	Comparison of the antiviral activity of flavonoids against murine norovirus and feline calicivirus	Article not related to the covid theme
278	Shahidi & Yeo (2018)	Bioactivities of phenolics by focusing on suppression of chronic diseases: A review	Article not related to the covid theme
279	Shao *et al* (2014)	Essential structural requirements and additive effects for flavonoids to scavenge methylglyoxal	Article not related to the covid theme
280	Shenvi *et al* (2013)	Synthesis, anticancer and antioxidant activities of 2,4,5-trimethoxy chalcones and analogues from asaronaldehyde: Structure-activity relationship	Article not related to the covid theme
281	Shi *et al* (2012)	Metabolism-based synthesis, biologic evaluation and SARs analysis of O-methylated analogs of quercetin as thrombin inhibitors	Article not related to the covid theme

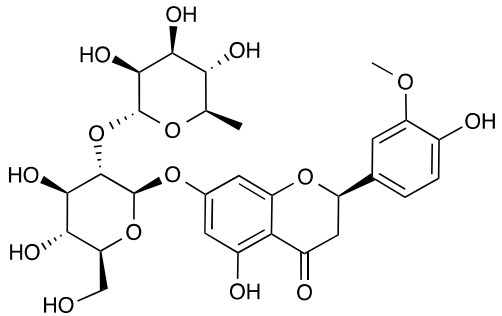
282	Shovlin & Vizcaychipi (2020)	Vascular inflammation and endothelial injury in SARS-CoV-2 infection: The overlooked regulatory cascades implicated by the ACE2 gene cluster	Article not related to the flavonoid theme
283	Siddiqui & Khan (2020)	Targeting SARS-CoV-2: Novel Source of Antiviral Compound(s) against COVID-19?	Article not original by design
284	Silfen *et al* (1988)	Bioflavonoid effects on in vitro cultures of Plasmodium falciparum. Inhibition of permeation pathways induced in the host cell membrane by the intraerythrocytic parasite	Article not related to the covid theme
285	Sinha *et al* (2020)	Potential Leads from Liquorice against SARS-CoV-2 Main Protease using Molecular Docking Simulation Studies	Article not related to the flavonoid theme
286	Song *et al* (2011)	Quercetin 7-rhamnoside reduces porcine epidemic diarrhea virus replication via independent pathway of viral induced reactive oxygen species	Article not related to the covid theme
287	Song *et al* (2016)	Integration of Multiple Analytical and Computational Tools for the Discovery of High-Potency Enzyme Inhibitors from Herbal Medicines	Article not related to covid and flavonoid theme
288	Spatafora & Tringali (2012)	Natural-derived polyphenols as potential anticancer agents	Article not related to the covid theme
289	Stringano *et al* (2011)	Deciphering the complexity of sainfoin (Onobrychis viciifolia) proanthocyanidins by MALDI-TOF mass spectrometry with a judicious choice of isotope patterns and matrixes	Article not related to covid and flavonoid theme
290	Su *et al* (2020)	Network pharmacology study of Yinqiao Jiedu Soft Capsules in treatment of COVID-19	Article not related to flavonoid theme
291	Survay *et al* (2011)	New genera of flavonols and flavonol derivatives as therapeutic molecules	Article not related to the covid theme
292	Takeda *et al* (2013)	Theaflavins, dimeric catechins, inhibit peptide transport across Caco-2 cell monolayers via down-regulation of AMP-activated protein kinase-mediated peptide transporter PEPT1	Article not related to the covid theme
293	Takeda *et al* (2020)	Saxifraga spinulosa-Derived Components Rapidly Inactivate Multiple Viruses Including SARS-CoV-2	Article not related to the flavonoide theme
294	Tang *et al* (2019)	Preventive agents for neurodegenerative diseases from resin of Dracaena cochinchinensis attenuate LPS-induced microglia over-activation	Article not related to the covid theme
295	Taylor *et al* (2003)	Hop (Humulus lupulus L.) proanthocyanidins characterized by mass spectrometry, acid catalysis, and gel permeation chromatography	Article not related to the covid theme
296	Theoharides (2020)	COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin	Article not original by design
297	Theoharides & Conti (2020)	Dexamethasone for COVID-19? Not so fast	Article not original by design
298	Thieury *et al* (2017)	Mechanisms of action and structure-activity relationships of cytotoxic flavokawain derivatives	Article not related to the covid theme
299	Tian (2006)	Inhibition of fatty acid synthase by polyphenols	Article not related to the covid theme

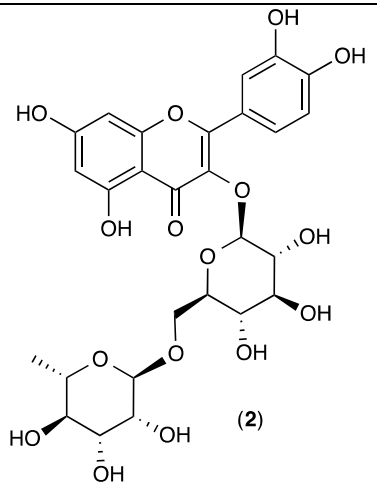
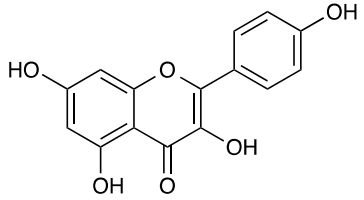
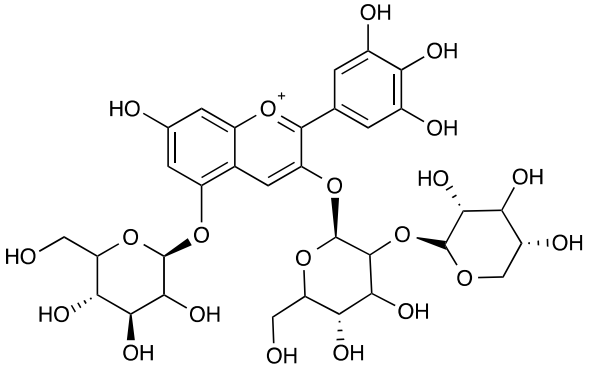
300	Touil *et al* (2009)	Flavonoid-induced morphological modifications of endothelial cells through microtubule stabilization	Article not related to the covid theme
301	Tsujita *et al* (2013)	α-Amylase inhibitory activity from nut seed skin polyphenols. 1. Purification and characterization of almond seed skin polyphenols	Article not related to the covid theme
302	Tu *et al* (2015)	Study of the structure-activity relationship of flavonoids based on their interaction with human serum albumin	Article not related to the covid theme
303	Tu *et al* (2015)	Understanding the structure-activity relationship between quercetin and naringenin: In vitro	Article not related to the covid theme
304	Tu *et al* (2016)	Structure-activity relationship study between baicalein and wogonin by spectrometry, molecular docking and microcalorimetry	Article not related to the covid theme
305	Tutunchi *et al* (2020)	Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19	Article not original by design
306	Ur Rashid *et al* (2019)	Promising anti-inflammatory effects of chalcones via inhibition of cyclooxygenase, prostaglandin E(2), inducible NO synthase and nuclear factor κb activities	Article not related to the covid theme
307	Van Hamme *et al* (2008)	Clathrin- and caveolae-independent entry of feline infectious peritonitis virus in monocytes depends on dynamin	Article not related to the covid theme
308	Wang *et al* (2005)	Neuroactive flavonoids interacting with GABAA receptor complex	Article not related to the covid theme
309	Wang *et al* (2009)	Evaluation for inhibitory effects of natural flavonoids on neuraminidases	Article not related to the covid theme
310	Wang *et al* (2010)	Interaction of benzopyranone derivatives and related compounds with human concentrative nucleoside transporters 1, 2 and 3 heterologously expressed in porcine PK15 nucleoside transporter deficient cells. Structure-activity relationships and determinants of transporter affinity and selectivity	Article not related to the covid theme
311	Wang *et al* (2010)	Flavonoids from Dracocephalum tanguticum and their cardioprotective effects against doxorubicin-induced toxicity in H9c2 cells	Article not related to the covid theme
312	Wang *et al* (2011)	Estimation of daily proanthocyanidin intake and major food sources in the U.S. diet	Article not related to the covid theme
313	Wang *et al* (2014)	Dietary flavonoids modulate CYP2C to improve drug oral bioavailability and their qualitative/quantitative structure-activity relationship	Article not related to the covid theme
314	Wang *et al* (2016)	Design, synthesis and activity of novel sorafenib analogues bearing chalcone unit	Article not related to the covid theme
315	Wang *et al* (2019)	An update on polyphenol disposition via coupled metabolic pathways	Article not related to the covid theme
316	Wei *et al* (2016)	Inhibition of Monoamine Oxidase by Stilbenes from Rheum palmatum	Article not related to the covid theme
317	Williamson & Kerimi (2020)	Testing of natural products in clinical trials targeting the SARS-CoV-2 (Covid-19) viral spike protein-angiotensin converting enzyme-2 (ACE2) interaction	Article not original by design

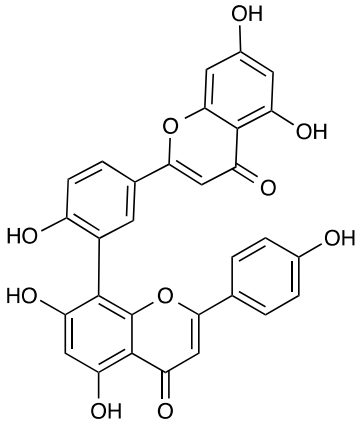
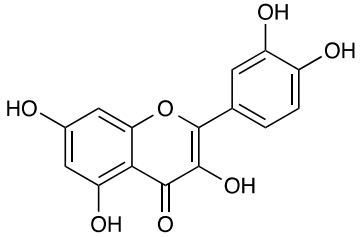
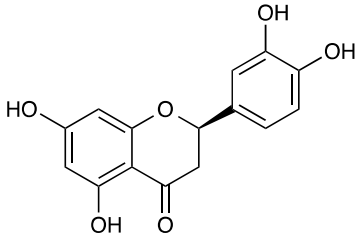
318	Wisnuwardani *et al* (2019)	Estimated dietary intake of polyphenols in European adolescents: the HELENA study	Article not related to the covid theme
319	Woo *et al* (2012)	Flavanones inhibit the clonogenicity of HCT116 cololectal cancer cells	Article not related to the covid theme
320	Wu *et al* (2003)	Chemical and pharmacological investigations of Epimedium species: A survey.	Article not related to the covid theme
321	Xu *et al* (2007)	Structure-activity relationships of flavonoids for vascular relaxation in porcine coronary artery	Article not related to the covid theme
322	Yadav *et al* (2013)	Screening of flavonoids for antitubercular activity and their structure-activity relationships	Article not related to the covid theme
323	Yamauchi *et al* (2018)	Selective synthesis of 7-O-substituted luteolin derivatives and their melanonenesis and proliferation inhibitory activity in B16 melanoma cells	Article not related to the covid theme
324	Yan *et al* (2020)	The structure-activity relationship review of the main bioactive constituents of Morus genus plants	Article not related to the covid theme
325	Yang *et al* (2011)	Green tea polyphenols as proteasome inhibitors: Implication in chemoprevention	Article not related to the covid theme
326	Yang *et al* (2019)	Dietary Flavonoids Scavenge Hypochlorous Acid via Chlorination on A- and C-Rings as Primary Reaction Sites: Structure and Reactivity Relationship	Article not related to the covid theme
327	Yang *et al* (2020)	Development of a novel nitric oxide (NO) production inhibitor with potential therapeutic effect on chronic inflammation	Article not related to covid and flavonoid theme
328	Yang *et al* (2020)	Chemical composition and pharmacological mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against Coronavirus Disease 2019 (COVID-19): In silico and experimental study	Article not related to flavonoid theme
329	Ye *et al* (2014)	Bioactivity-guided isolation of anti-inflammation flavonoids from the stems of Millettia dielsiana Harms	Article not related to the covid theme
330	Yi *et al* (2004)	Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells	Article not related to the covid theme
331	Yu *et al* (2012)	Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13	Article not related to the covid theme
332	Zeouk *et al* (2020)	Sesquiterpenoids and flavonoids from Inula viscosa induce programmed cell death in kinetoplastids	Article not related to the covid theme
333	Zhang *et al* (2001)	O-H bond dissociation energies of phenolic compounds are determined by field/inductive effect or resonance effect? A DFT study and its implication	Article not related to covid and flavonoid theme
334	Zhang *et al* (2005)	Structure activity relationships and quantitative structure activity relationships for the flavonoid-mediated inhibition of breast cancer resistance protein	Article not related to the covid theme
335	Zhang *et al* (2012)	Herba epimedii flavonoids suppress osteoclastic differentiation and bone resorption by inducing G2/M arrest and apoptosis	Article not related to the covid theme

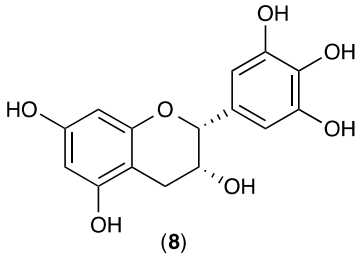
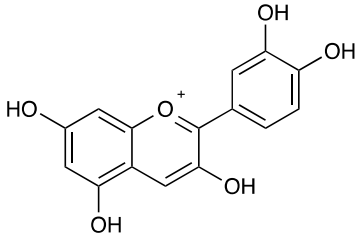
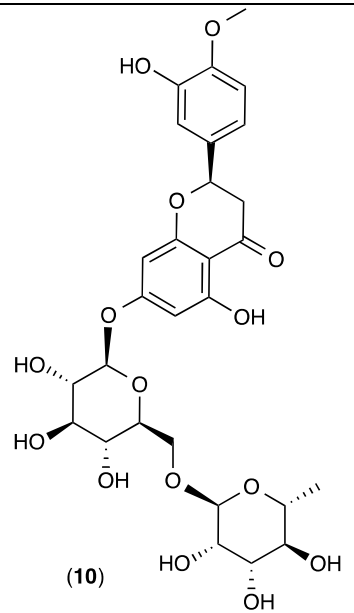
336	Zhang *et al* (2018)	A review on the structure–activity relationship of dietary flavonoids for protecting vascular endothelial function: Current understanding and future issues	Article not related to the covid theme
337	Zhang *et al* (2019)	Design, Synthesis and Investigation of the Potential Anti-Inflammatory Activity of 7-O-Amide Hesperetin Derivatives	Article not related to the covid theme
338	Zhang *et al* (2008)	Anticomplementary principles of a Chinese multiherb remedy for the treatment and prevention of SARS	Article not related to the covid theme
339	Zhao *et al* (2011)	Identification and initial SAR of silybin: An Hsp90 inhibitor	Article not related to the covid theme
340	Zhao *et al* (2017)	The Composition of the Mobile Phase Affects the Dynamic Chiral Recognition of Drug Molecules by the Chiral Stationary Phase	Article not related to the covid theme
341	Zhen *et al* (2017)	Synthesis of novel flavonoid alkaloids as α-glucosidase inhibitors	Article not related to the covid theme
342	Zheng *et al* (2014)	Synthesis and anti-cancer activities of apigenin derivatives	Article not related to the covid theme
343	Zhou *et al* (2013)	Chemical constituents of rhizome of Dasymaschalon trichophorum Mer	Article not related to the covid theme
344	Zhou *et al* (2020)	Chemical constitutents from flowers of Stellera chamaejasme and their antioxidant activity	Article not related to the covid theme
345	Zhuang *et al* (2020)	Can network pharmacology identify the anti-virus and anti-inflammatory activities of Shuanghuanglian oral liquid used in Chinese medicine for respiratory tract infection?	Article not related to flavonoid theme

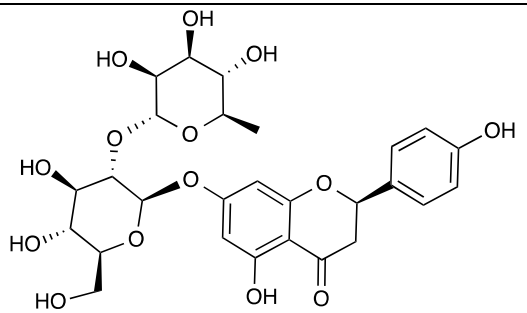
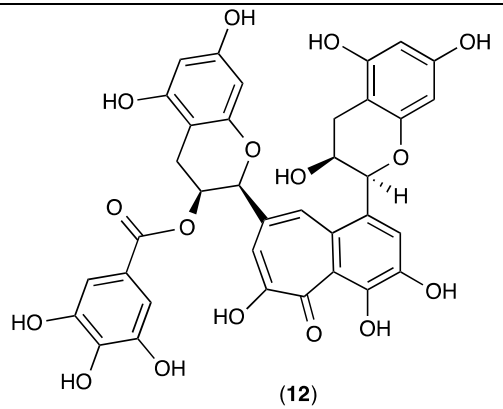
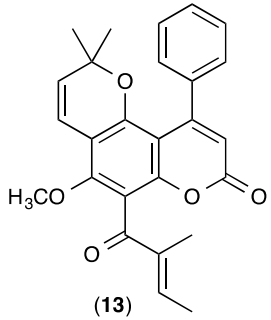
Appendix D - Table with the complete information from main flavonoid chemical structure.

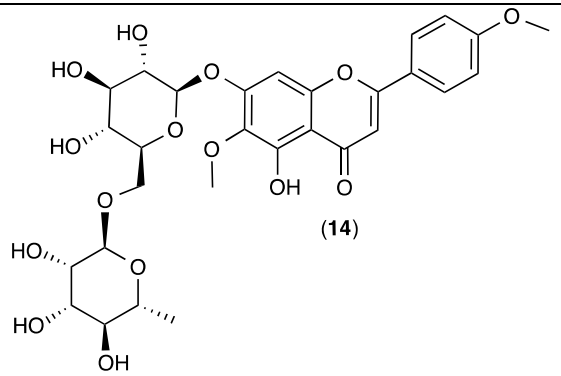
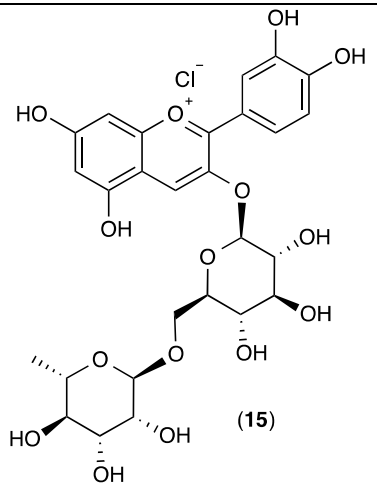
FLAVONOIDE	CLASS OF FLAVONOID	MOLECULAR FORMULA	STRUCTURE
Neohesperidin	Flavanone	$C_{28}H_{34}O_{15}$	 (**1**)

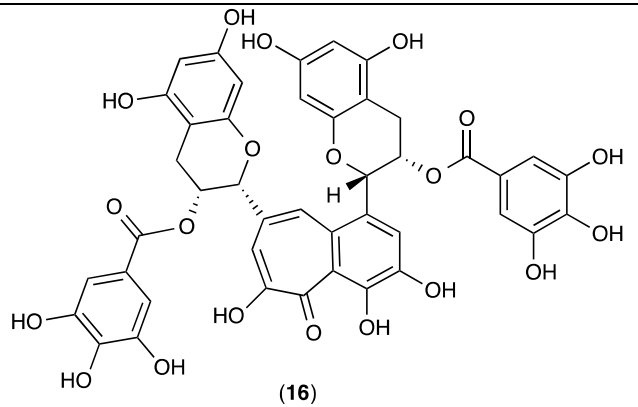
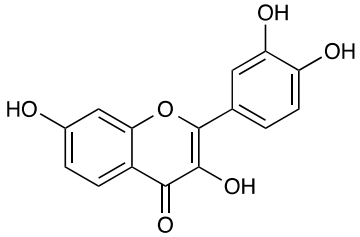
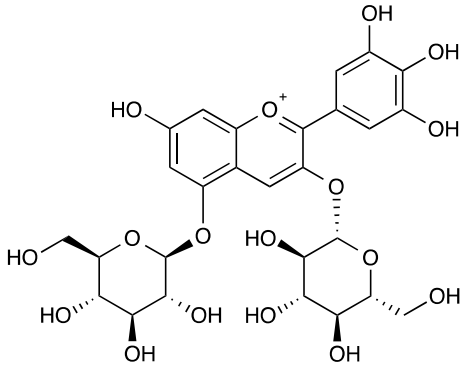
Rutin	Flavonol	$C_{27}H_{30}O_{16}$	 (**2**)
Kaempferol	Flavonol	$C_{15}H_{10}O_6$	 (**3**)
Delphinidin-3-sambubioside-5-glucoside	Anthocyanidin	$C_{32}H_{39}O_{21}^{+}$	 (**4**)

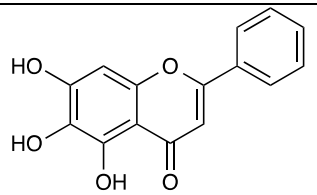
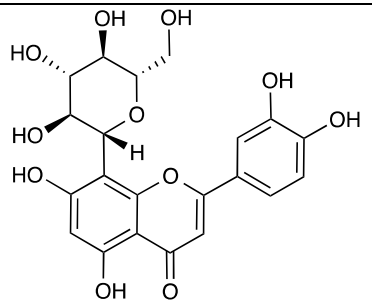
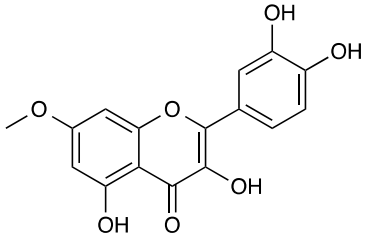
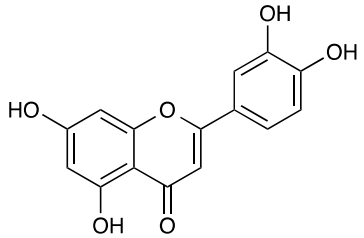
Amentoflavone	Biflavone	$C_{30}H_{18}O_{10}$	 (**5**)
Quercetin	Flavonol	$C_{15}H_{10}O_7$	 (**6**)
Eriodictyol	Flavanone	$C_{15}H_{12}O_6$	 (**7**)

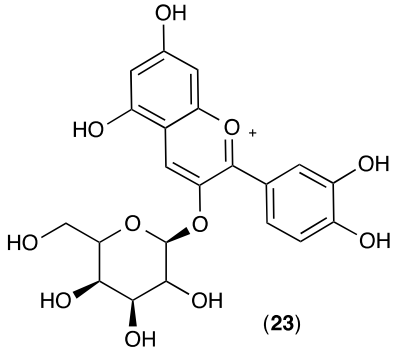
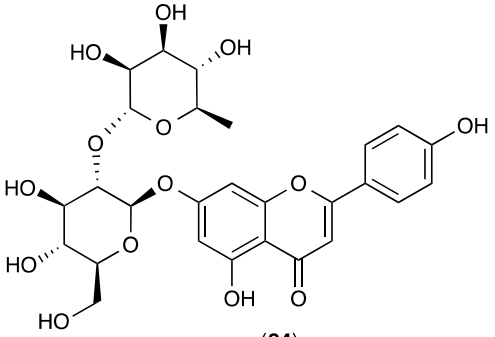
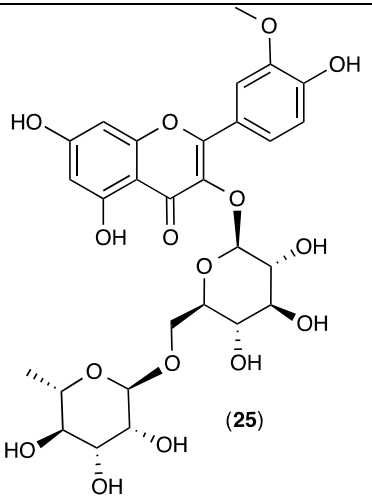
Epigallocatechin	Flavano	$C_{15}H_{14}O_7$	 (**8**)
Cyanidin	Anthocyanidin cation	$C_{15}H_{11}O_6^+$	 (**9**)
Hesperidin	Flavanone	$C_{28}H_{34}O_{15}$	 (**10**)

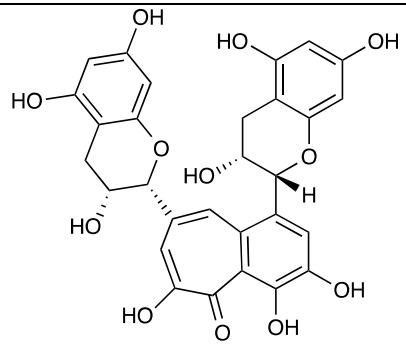
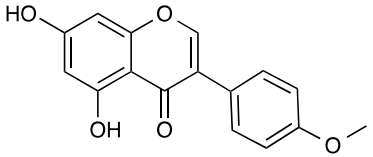
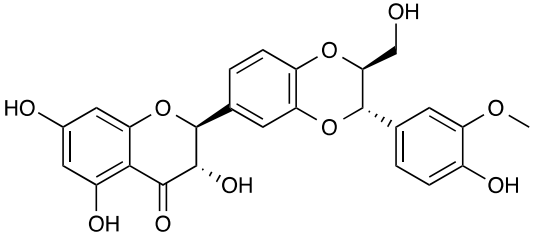
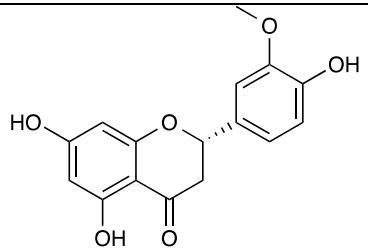
Naringin	Flavanone	$C_{27}H_{32}O_{14}$	 (**11**)
Theaflavin monogallate	Biflavonoid	$C_{36}H_{28}O_{16}$	 (**12**)
Calophyllolide	Neoflavonoid	$C_{26}H_{26}O_6$	 (**13**)

Pectolinarin	Flavone	$C_{29}H_{34}O_{15}$	 (**14**)
Cyanidin-3-rutinoside	Anthocyanidin	$C_{27}H_{31}O_{15}^{+}$	 (**15**)

Theaflavin-3,3'-digallate	Flavanol	$C_{43}H_{32}O_{20}$	 (**16**)
Fisetin	Flavonol	$C_{15}H_{10}O_6$	 (**17**)
Delphinidin-3,5-diglucoside	Anthocyanidin cation	$C_{27}H_{31}O_{17}^{+}$	 (**18**)

Baicalein	Flavone	$C_{15}H_{10}O_5$	 (**19**)
Orientin	Flavone	$C_{21}H_{20}O_{11}$	 (**20**)
Rhamnetin	Flavonol	$C_{16}H_{12}O_7$	 (**21**)
Luteolin	Flavone	$C_{15}H_{10}O_6$	 (**22**)

Cyanidin-3-glucoside	Anthocyanidin	$C_{21}H_{21}O_{11}^{+}$	 (**23**)
Rhoifolin	Flavone	$C_{27}H_{30}O_{14}$	 (**24**)
Narcissoside	Flavonol	$C_{28}H_{32}O_{16}$	 (**25**)

Theaflavin	Biflavonoid	$C_{29}H_{24}O_{12}$	 (**26**)
Biochanin A	Isoflavone	$C_{16}H_{12}O_5$	 (**27**)
Silymarin/ Silibinin (Silybin A)	Flavonolignan	$C_{25}H_{22}O_{10}$	 (**28**)
Hesperitin	Trihydroxyflavanone	$C_{16}H_{14}O_6$	 (**29**)

Anexo 1 Checklist Prisma-ScR

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	PAGE 22
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	PAGE 22
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	PAGE 24
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	PAGE 25
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	PAGE 25
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	PAGE 26
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	PAGE 26
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	PAGE 70
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	PAGE 67
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	PAGE 26
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	PAGE 68
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	PAGE 68
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	PAGE 26

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESUL TS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	PAGE 26
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	PAGE 29
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	PAGE 36
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	PAGE 29
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	PAGE 38
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	PAGE 44
Limitations	20	Discuss the limitations of the scoping review process.	PAGE 49
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	PAGE 50
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	PAGE 50

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.