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Can propolis and their compounds be efficacy in the treatment of coronavirus disease 2019 (COVID-19)? A systematic review

A própolis e seus compostos podem ser eficazes no tratamento da doença do coronavírus 2019 (COVID-19)? Uma revisão sistemática

¿Pueden los propóleos y sus compuestos ser efectivos en el tratamiento de la enfermedad por Coronavirus 2019 (COVID-19)? Una revisión sistemática

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Abstract
Despite the advancement of vaccination and the reduction in the number of deaths, there is still the emergence of new variants, such as the omicron of SARS-CoV-2 (COVID-19). In this sense, new natural antiviral therapies are highly explored. One of these products, propolis, have shown promising results against COVID-19, including the inhibition of the binding between the coronavirus and ACE2. This systematic review aimed to gather a summary of scientific evidence existing on the effective of the therapeutic use of propolis and their components in the treatment of COVID-19. The protocol for the present systematic review was registered on the PROSPERO (CRD42021267016). In this study, we analyzed 185 articles, selecting 13 of them. Some phenolic compounds and flavonoids, such as artepillin C, hesperetin, CAPE and rutin, were widely cited, as they have great potential for binding with the molecular targets of SARS-CoV-2. Some clinical studies that evaluated the effects of propolis against COVID-19 were included, and confirmed the effectiveness of propolis and its components. The results of this review demonstrate the effectiveness of using propolis and their components in the treatment of COVID-19 due to its antiviral activities. Additionally, the anti-inflammatory and immunomodulatory properties can help to patients with COVID-19.
Keywords: SARS-CoV-2; Rutin; Quercetin; CAPE; Systematic Review; Health teaching.

Resumo

Apesar do avanço da vacinação e da redução do número de óbitos, ainda há o surgimento de novas variantes, como a ômicron do SARS-CoV-2 (COVID-19). Nesse sentido, novas terapias antivirais naturais são altamente exploradas. Um desses produtos, a própolis, tem mostrado resultados promissores contra o COVID-19, incluindo a inibição da ligação entre o coronavírus e a ECA2. Esta revisão sistemática teve como objetivo reunir um resumo das evidências científicas existentes sobre a eficácia do uso terapêutico da própolis e seus componentes no tratamento da COVID-19. O protocolo da presente revisão sistemática foi registrado no PROSPERO (CRD42021267016). Neste estudo, analisamos 185 artigos, selecionando 13 deles. Alguns compostos fenólicos e flavonoides, como artepillina C, hesperetina, CAPE e rutina, foram amplamente citados, pois possuem grande potencial de ligação com os alvos moleculares do SARS-CoV-2. Alguns estudos clínicos que avaliaram os efeitos da própolis contra a COVID-19 foram incluídos e confirmaram a eficácia da própolis e seus componentes. Os resultados desta revisão demonstram a eficácia do uso da própolis e seus componentes no tratamento da COVID-19 devido às suas atividades antivirais. Além disso, as propriedades anti-inflamatórias e imunomoduladoras podem ajudar pacientes com COVID-19.

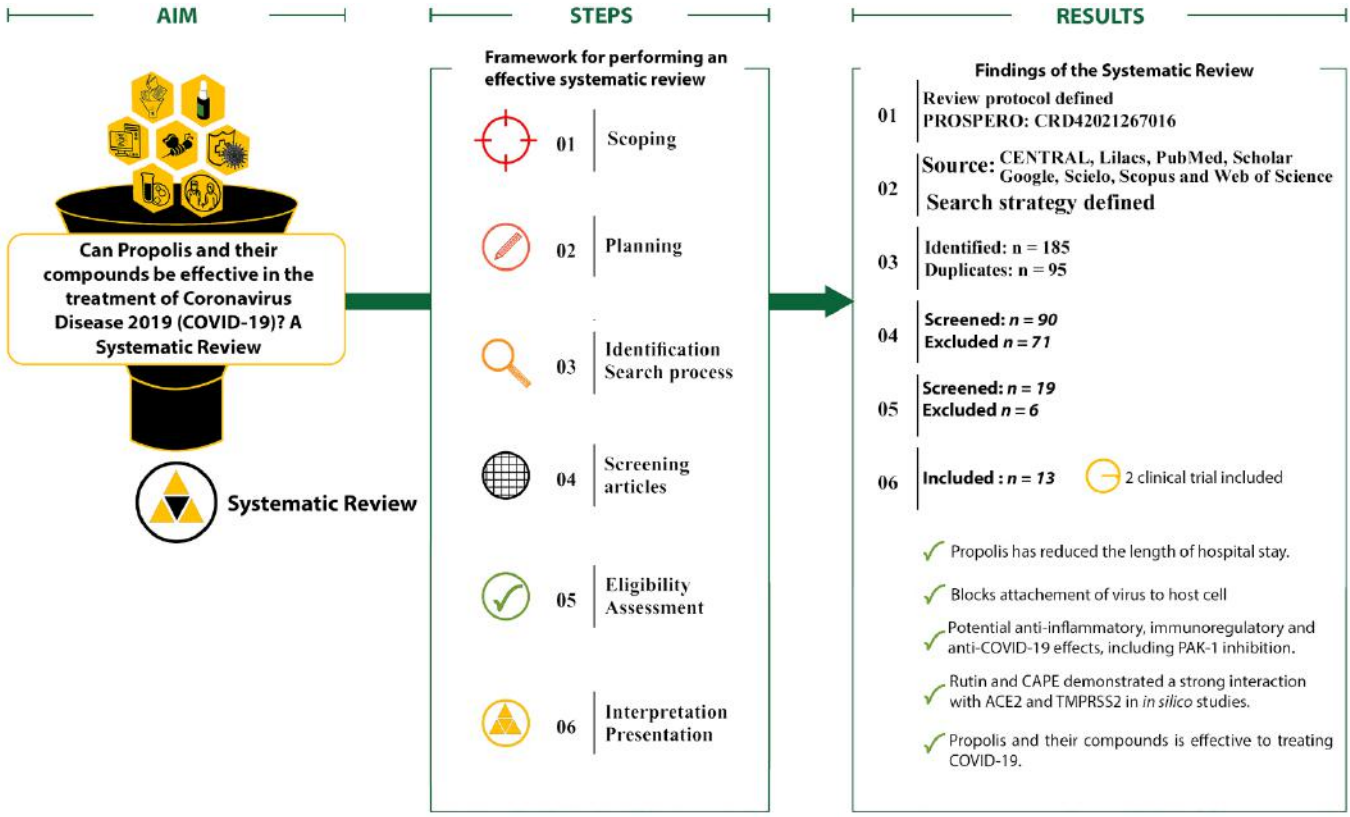
Palavras-chave: SARS-CoV-2; Rutina; Quercetina; CAPE; Revisão Sistemática; Ensino em saúde.

Resumen

A pesar del avance de la vacunación y la reducción en el número de muertes, todavía está surgiendo nuevas variantes, como el omicrón SARS-CoV-2 (COVID-19). En este sentido, las nuevas terapias antivirales naturales están muy exploradas. Uno de esos productos, el propóleo, ha mostrado resultados prometedores contra el COVID-19, incluida la inhibición del vínculo entre el coronavirus y la ACE2. Esta revisión sistemática tuvo como objetivo recopilar un resumen de la evidencia científica existente sobre la efectividad del uso terapéutico del propóleo y sus componentes en el tratamiento de la COVID-19. El protocolo de la presente revisión sistemática se registró en PROSPERO (CRD42021267016). En este estudio analizamos 185 artículos, seleccionando 13 de ellos. Algunos compuestos fenólicos y flavonoides, como la artepilina C, la hesperetina, la CAPE y la rutina, fueron ampliamente citados, ya que tienen un gran potencial para unirse a los objetivos moleculares del SARS-CoV-2. Se incluyeron algunos estudios clínicos que evaluaron los efectos del propóleo contra el COVID-19 y confirmaron la efectividad del propóleo y sus componentes. Los resultados de esta revisión demuestran la efectividad del uso de propóleos y sus componentes en el tratamiento de la COVID-19 debido a sus actividades antivirales. Además, las propiedades antiinflamatorias e inmunomoduladoras pueden ayudar a los pacientes con COVID-19.

Palabras clave: SARS-CoV-2; Rutina; Quercetina; CAPE; Revisón Sistemática; Enseñanza en salud.

Graphical abstract



Source: Authors.

1. Introduction

Despite the advancement of vaccination and the reduction in the number of deaths, there is still the emergence of new variants, such as omicron of SARS-CoV-2 (COVID-19). In this sense, the rapid evaluation of possible resistance to anti-viral therapies and vaccines is highly required. However, data on the efficacy of available therapeutic agents and vaccines is clearly insufficient (Drożdżal *et al*., 2021; Yao *et al*., 2020).

SARS-CoV-2 infection is initiated by binding of a viral protein spike to the angiotensin II-converting enzyme receptor (ACE2) on the surface of the host cell, fusing with the cell membrane and releasing viral RNA. Activation of viral proteins is mediated by proteases, such as transmembrane serine protease 2 (TMPRSS2) (Hoffmann *et al*., 2020). After infection, the new coronavirus is able to positively regulate p21-activated kinase 1 (PAK1), which mediates several critical mortality factors, such as inflammation and pulmonary fibrosis. Increased levels of PAK1 can also suppress the adaptive immune response and thus facilitate viral replication (Maruta & He, 2020). SARS-CoV-1 infection is associated with increased levels of activated pro-inflammatory chemokines and cytokines leading to the development of atypical pneumonia, with rapid respiratory impairment and lung failure (Ding *et al*., 2004).

Natural products are among the options explored, as many of them have shown the capability of affecting various metabolic pathways in humans and microorganisms, with anti-inflammatory, antiviral and immunomodulatory activities. One of these products, propolis, a resinous compound produced by bees with a variable composition influenced by environmental factors (Bachevski *et al*., 2020). have shown promising results against COVID-19 (Berretta *et al*., 2020), including the inhibition of the binding between the coronavirus and ACE2 (Khayrani *et al*., 2021).

Quercetin, one of the major flavonoids found in propolis, was able to inhibit the protease enzymes from the SARS-CoV-1 and MERS-CoV viruses *in vitro* (Rocha *et al*., 2013). In addition, as coronaviruses modulate the cellular unfolded protein response (UPR) to complete their replication cycle, quercetin may interfere with this pathway (Polansky & Lori, 2020).

Another promising pharmacological approach to propolis in the treatment of COVID-19 is to target downstream effectors, such as p21-activated kinases (PAKs). Caffeic acid phenethyl ester (CAPE) demonstrated the potential to block viral infection and negatively regulate ras related C3 botulinum toxic substrate (RAC). The practical aspect of those results is that propolis may be a useful drug to prevent coronavirus-induced lung fibrosis (Maruta & He, 2020).

Recent reviews have highlighted the potential benefits of propolis overall and specifically against COVID-19. Ripari *et al*. (2021) reviewed *in vitro* and preclinical trials to substantiate anti-inflammatory, immunomodulatory and antiviral activities. Berretta *et al*. (2020) reviewed the use of propolis against SARS-CoV-2 and highlighted previous *in silico* and *in vitro* studies of its antiviral and immunomodulatory properties showing, however, no results from clinical trials. Arentz *et al*. (2021) performed a rapid review of clinical studies on the effects of honeybee products on respiratory tract diseases, including COVID-19. However, there was 1 article in COVID-19. Yosri *et al*. (2021) performed a review of *in silico*, preclinical and clinical applications of propolis on respiratory tract diseases, including COVID-19. However, these authors were published before the results of clinical trials using propolis against COVID-19, cited in our review.

Propolis has also demonstrated an antiviral effect, *in vivo* and *in vitro* studies, against the *influenza* virus (Shimizu *et al*., 2008), human rhinovirus (Kwon *et al*., 2020) and human respiratory diseases (Takeshita *et al*., 2013). This antiviral activity is associated with the presence of phenolic compounds, which are able to block or reduce the adsorption and entry of the virus in host cells (Kwon *et al*., 2020; Lima *et al*., 2021). Furthermore, propolis is a stimulant of the adaptive immune system, which can reinforce its prophylactic antiviral effect (Babaei *et al*., 2016; Lima *et al*., 2021). Governa *et al*. (2019) reported that propolis was able to reduce the key protein (neuraminidase) for the entry of the H_1N_1 virus into cells, and can be an important antiviral agent. Finally, Wang *et al*. (2021) reported that the propolis ameliorates pulmonary fibrosis through Akt activation and regulates the protein expression of PPARγ (Kao *et al*., 2013).

Kwon *et al*. (2020) showed a superior antiviral activity of some propolis compounds (kaempferol, quercetin, chrysin and luteolin) in relation to ribavirin against rhinoviruses, which cause 50% of common colds across the globe. In addition, kaempferol and p-coumaric acid were able to reduce the levels of RNA replication when administered within 4 h after inoculation of the virus.

The present systematic review had the guiding question: "*Is the use of propolis and their components are efficient in the treatment of COVID-19?*" Thus, this systematic review aimed to gather a summary of scientific evidence existing between December 2019 and April 1, 2021, to confirm the effectiveness of propolis and their compounds in the treatment of COVID-19.

2. Methodology

The present systematic review had the guiding question: "*Is the use of propolis and its components are efficacy in the treatment of COVID-19*?". To search for the answer, it was decided to develop a systematic literature review. The protocol for the present systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO, protocol number CRD42021267016) (Sobrinho *et al*., 2021a). This study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher *et al*., 2015).

2.1 Search Strategy

We conducted a search for articles using the databases Cochrane Central Register of Controlled Trials (CENTRAL), Lilacs, PubMed, Scielo, Scholar Google, Scopus and Web of Science, type of document or language. The dates of search and the search criteria by databases are described in Table S1. All supplementary data was available on Mendeley Data (https://doi.org/10.17632/tcyrmp43f6) (Sobrinho *et al*., 2021b). The last search was completed on April 1, 2021 (dez/2021 to April/2021).

2.2 Selection of Relevant Articles

Articles that evaluated the use of propolis and their components in the treatment of COVID-19 in clinical trials, *in vivo*, *in vitro* and *in silico* studies were included. Papers published in Spanish, English and Portuguese were considered eligible. Reviews, case reports, protocol of study, clinical trials protocols, editorials and studies published in summary form and articles that were inaccessible, even after attempts to contact the corresponding author, were excluded.

2.3 Selection of Studies and Data extraction

Duplicate studies were excluded using reference managers (Mendeley Desktop® and JabRef). The extracted citations were imported into the Rayyan systematic review (https://rayyan.qcri.org/) (Ouzzani *et al*., 2016) for inclusion or exclusion based on the defined criteria.

The eligibility process was conducted in two separate stages. First, two researchers (BCA, and IRM or RCSS) independently screened all non-duplicate articles and excluded non-relevant articles based on title and/or abstract. A final list was agreed on, with discrepancies resolved by a third researcher (JMDA, CFO or BJMS). Second, full-text versions of the studies selected from stage 1 screening were downloaded and independently assessed for eligibility by the two researchers. Any discrepancies were resolved by a third researcher. Final decisions of stage 1 regarding inclusion of studies in the review were made by consensus, and the agreement between the two reviewers was analyzed by using the Kappa Test (Landis & Koch, 1977).

The collected data were author, year of publication, location of the study, composition of the extracts, type of study, objective of the study, results found and limitations. *In silico* studies were collected based on data related to binding affinity,

compounds, anti-covid-19 effect (*in vitro* assay), protein and/or receptor evaluated, methodological approach, software and model evaluation. In clinical studies, the numbers of participants, parameters evaluated and anti-covid-19 effect were collected.

2.4 Risk of Bias of included clinical studies

The quality of the studies was evaluated using the Jadad Scale (Jadad *et al*., 1996). In addition, the risk of bias for each reference included in the systematic-review was assessed using the Cochrane Risk of Bias Tool (J. Higgins & Green, 2015).

3. Results and Discussion

3.1 Search strategy

The initial research identified 185 records. First, duplicate records were removed (n = 95), excluded by reading the title and/or abstract (n = 71; kappa test = 0.431±0.09) and excluded after reading the articles (n = 6). Finally, 13 articles were selected. Figure 1 reports the PRISMA flowchart detailing the screening process.

3.2 Characteristics of studies included

The 13 reports found in the search strategy step, 11 have *in silico* studies, which differ in the type of propolis extract, their compounds and/or target proteins. In addition, among the five clinical trials records found in the ClinicalTrial.gov database, only two responded to contact with the publication submission and/or main results. Both clinical trials (Kosari *et al*., 2021; Silveira *et al*., 2021) scored as low quality on the Jadad scale and low risk of bias in the Cochrane Risk of Bias tool. The relevant results and characteristics of the studies are described in Table 1, 2 and 3.

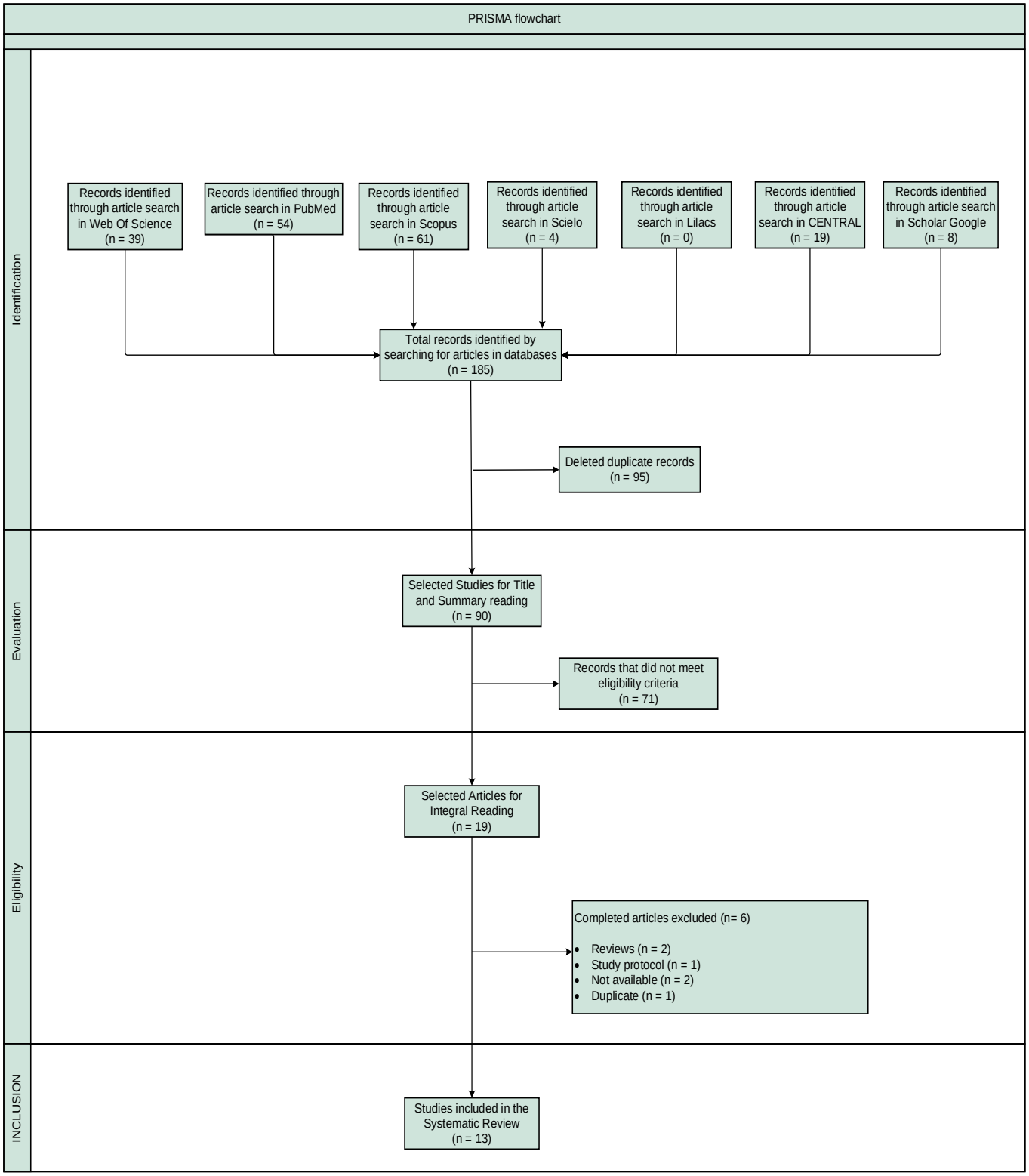
3.3 Results of the Systematic review

3.3.1 In silico studies

These studies were carried out with different approaches of docking, virtual screening and molecular dynamics. Table S2 summarizes the major relevant results and findings obtained from these studies, while Table S3 contains all extracted data.

This section highlighted the specific interaction of propolis and their components on the targets of SARS-CoV-2. Molecular docking is a suitable computational tool to describe the affinity between a ligand and biomacromolecule; and its respective pharmacophoric pose into the binding site (Maia *et al*., 2020; Meng *et al*., 2012). In other words, docking has two tasks to solve, the first is the determination of each intramolecular interaction, resulting in an affinity measure; the second one, is the determination of the correct pose of ligand into the binding site, which docking methods have to be able to reproduce the conformation crystallographic ligand of a specific molecular target. The obtention of affinity values, described by binding energy or scores, have permitted the ranking of a set of ligands. Thus, only the most promising compounds are selected and addressed to experimental work. In the case of all methods described by this review, the lowest values indicate a high affinity for the molecular target. Noteworthy that different force fields can reach different results due their own parametrization process. Consequently, they cannot be compared directly due to the difference in the order of magnitude. The docking process is beyond the scope of this review; however, it can be clarified.

Figure 1. PRISMA Flowchart reporting the study screening process.



Source: Authors.

3.3.2 Interaction of propolis components with main protease (M^{pro})

3CL-protease (M^{pro}) is the enzyme responsible for processing viral polyproteins (Refaat *et al*., 2021) and its inhibition can block viral replication (Sahlan *et al*., 2021). Propolis components were selected using the Lipinski's rule of five (RO5) (Lipinski *et al*., 2012) and evaluated for their potential inhibition of M^{pro}, comparing those components with the crystallographic

ligand of α-ketoamide 13b (PDB ID: 6Y2F). The results of this study suggested that broussoflavonol F, glyasperin A and sulabiroin A are able to interact with the catalytic sites of M^{pro} and bind with 75%, 63% and 44% similarity, respectively, in comparison with the crystallographic ligand (Sahlan *et al*., 2021). In another study conducted in India, 4 out of 6 compounds (CAPE, caffeic acid, chrysin and galagin) showed affinity by the receptor suggesting a potential to inhibit M^{pro} from SARS-CoV-2 (Hashem, 2020). However, none of these studies were evaluated properly using tools such as redocking, roc curve, molecular dynamics or preclinical and clinical studies, so there is no guarantee that they obtained false positive results.

All the 10 components evaluated showed less binding affinity than remdesivir. Interestingly, rutin and CAPE showed greater binding affinity than hydroxychloroquine, and rutin showed the best binding affinity among propolis compounds (Refaat *et al*., 2021).

Kumar *et al*. (2020) demonstrated the CAPE inhibitory potential for M^{pro} of SARS-CoV-2 with results similar to its tested crystallographic inhibitor (N3). These results showed CAPE can be a lead compound to develop a new drug for the treatment of

COVID-19 (Kumar, Dhanjal, Kaul, et al., 2020). Noteworthy, CAPE has a Michael acceptor moiety, which can react with others coronavirus proteases as described.

3.3.3 Interaction of propolis compounds with TMPRSS2

The potential inhibitor of TMPRSS2 for CAPE was slightly greater than its known inhibitor (camostat mesylate).(Kumar, Dhanjal, Bhargava, et al., 2020) In other words, Michael acceptor moiety of CAPE can interact with different proteases showing a non-selective compound.

3.3.4 Interaction of propolis compounds with ACE2

Khayrani *et al*. (2021) evaluated the potential of propolis compounds to modulate ACE2 and thus inhibit receptor binding with SARS-CoV-2. The results showed that five compounds (glucosperin A, broussoflavonol F, sulabiroins A, (2)-5,7-dihydroxy-4'-methoxy-8-prenylflavonone A isorhamnetin) has the potential to inhibit the binding of the virus to ACE2. The docking scores obtained are more favorable than a tested potent inhibitor (MLN-4760). However, taking into account the similarity of binding, two compounds (isorhamnetin and glucosperin A) were considered to have the greatest potential (Khayrani *et al*., 2021). As described previously, the docking methodologies should reproduce the pose of crystallographic ligand. Thus, the first approach is called redocking. Redocking consists in the removal of crystallographic ligand of the binding site following its docking. This redocking process shows: i) the binding energy of crystallographic ligands; ii) if the docking parameters are suitable; and iii) the docking methodology can reproduce the crystallographic pose of the ligand. Thus, the determination of root means square deviation (RMSD) between the atomic position of crystallographic ligand and redocking ligand should be less than 2.0 Å (Maia *et al*., 2020; Meng *et al*., 2012). Thus, even though the redocking process was carried out by these papers, the RMSD was not described, beyond others evaluation methods, such as roc curve or molecular dynamics simulations.

Güler *et al*. (2020) also evaluated the ability of flavonoids present in propolis to bind to ACE2 receptors. According to the docking analysis, it was demonstrated that rutin, myricetin, CAPE, hesperetin and pinocembrin showed the best potential for inhibition compared to the natural inhibitor (MLN-4760). Therefore, it is considered that rutin can compete with SARS-CoV-2

Table 1. Relevant results of *in silico* and *in vitro* studies on effectiveness of propolis from different regions of the world in the treatment of COVID-19. Papers collected in dez/2021 to April/2021.

Propolis source	Country	Type of study	Objective	Outcome	Limitation	Study
Anatolian própolis	Turkey	*In silico* and i*n vitro*	To evaluate whether ethanolic extracts of propolis from Anatolia inhibit the COVID-19 virus in terms of binding of the S1 spike protein and the ACE2 receptor in both *in vitro* and *in silico* studies.	• Pinocembrine, chrysin, caffeic acid phenethyl ester and hesperetin had very low free binding energies to the ACE2 receptor and the SARS-CoV-2 RBD peak protein. • These four flavonoids were also found to have greater binding potential than hydroxychloroquine. • Hesperetin is the best inhibitor of *spike* protein of SARS-CoV-2 and ACE2, has the lowest IC_{50} value (16.88 mM), pinocembrine and CAPE were followed. • Pinocembrine had a high inhibitory effect in the *in silico* study, while hesperetin was more active in the *in vitro* study.	• More detailed studies are needed.	Güler et al. (2020)
Brazilian green propolis	Canada	*In silico*	Find molecules containing amino acid substituents that mimic the SLiM responsible for recruiting host PP2A-B56.	• LxxLxE-like motifs from CoV-2 allowed us to find a small molecule called Artepillin C, which is known to have anti-inflammatory activity.	• Clinical studies are needed.	Maaroufi (2020)
Egyptian própolis	Egypt	*In silico*	Comparative analysis of chemical composition between samples collected in different locations in Egypt with analysis concomitant with anti-COVID-19 activity.	• The results of docking studies showed that most compounds had promising binding scores.	• Some Egyptian propolis compounds are excellent candidates for combating COVID-19.	Elwakil et al. (2021)
Egyptian propolis	Egypt	*In silico* and i*n vitro*.	Develop liposomal formulation optimized to enhance the antiviral activity of propolis against COVID-19.	• All Egyptian propolis flavonoid compounds have binding affinity to the M^{pro} and *spike* protein compared to Avigan, hydroxychloroquine and Remdesivir. • Liposomal formulation can guarantee delivery to target cells.	• Clinical studies are needed to estimate the effectiveness of the formulation.	Refaat et al. (2021)
Propolis (PT Nano Herbaltama Internasional)	Indonesia	*In silico*	Investigate the interaction of the active molecular compounds of propolis against the main protease and protein spike of SARS-CoV-2 by molecular docking approach.	• The candidate to inhibit M^{pro} of SARS-CoV-2 was methylphiopogonone A, 3'-methoxyididine and genistin. • Neoblavaisoflavone, methylphiopogonone A, 3′-methoxyidaidzine and genistin) have lower binding affinity energy than pravastatin (control), making these compounds candidates for *spike* protein inhibition.	• More *in vivo* studies are needed.	Harisna et al. (2021)
Sudawesi própolis	Indonesia	*In silico*	Evaluate the potency of Sulawesi's propolis compounds as ACE2 inhibitors.	• Glicosperina A, broussoflavonol F, sulabiroinas A, (2S) -5,7-dihydroxy-4′-methoxy-8-prenylflavanone, and isorhamnetina are potential to inhibit the binding of ACE-2 and SARS-CoV-2.	• Clinical studies are needed.	Khayrani et al. (2021)
Sudawesi propolis	Indonesia	*In silico*	Analyze molecular interactions between selected compounds of propolis Sulawesi produced by *Tetragonula sapiens* and the M^{pro} of SARS-CoV-2.	• Brousse flavonol F, glucosperin A and sulabiroins A are able to bind to the M^{pro} of SARS-CoV-2.	• Studies are needed to assess the potency and safety of broussoflavonol F and glucosperin A	Sahlan et al. (2021)
Turkish própolis	Turkey	*In silico*	Calculate the inhibition constants of some flavonoids, one of the active ingredients of propolis from Anatolia, to the enzyme ACE2 by molecular modeling with a positive control	• The high binding constants for ACE2 receptors and flavanones in the propolis ethanolic extract make it a good competitive inhibitor and natural protector of agents for the treatment of COVID-19.	• This study should be supported by further studies *in vivo*.	Guler et al. (2021)

NI: Not informed; ACE2: Angiotensin II-converting enzyme receptor; TMPRSS2: Transmembrane serine protease 2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; CAPE: Caffeic acid phenethyl ester; M^{pro}: main protein. Source: Authors.

Table 2. Relevant results of *in silico* studies on effectiveness of compounds of propolis from different regions of the world in the treatment of COVID-19. Papers collected in Dez/2021 to April/2021.

Compounds	Country	Objective	Outcome	Limitation	Study
3-phenyllactic acid, CAPE, caffeic acid, chrysin, galangin and lumichrome	Egypt	To evaluate the activity of six active compounds of bee product and propolis to inhibit the main protease of COVID-19	• CAPE, Chrysin, Galangin and Lumichrome are linked with good glide scores and can inhibit the M^{pro} and virus replication of COVID-19.	• More *in vivo* studies are necessary	Hashem et al. (2020)
CAPE	India	Examine the inhibitory potential of three natural compounds CAPE for TMPRSS2.	• CAPE have the same binding affinity for TMPRSS2 as Camostat mesylate.	• Clinical studies are needed.	Kumar, Dhanjal, Bhargava, et al. (2020)
CAPE	India	Examine the potential for binding CAPE to M^{pro} of SARS-CoV-2	• Strong possibility that CAPE have an inhibitory potential for the M^{pro} of SARS-CoV-2	• Studies are need experimental validation and clinical studies	Kumar, Dhanjal, Kaul, et al. (2020)

NI: Not informed; ACE2: Angiotensin II-converting enzyme receptor; TMPRSS2: Transmembrane serine protease 2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; CAPE: Caffeic acid phenethyl ester; M^{pro}: main protein. Source: Authors.

Table 3. Relevant results of clinical trials on effectiveness of propolis from different regions of the world in the treatment of COVID-19. Papers collected in dez/2021 to April/2021.

Propolis source	Country	Sample and design	Objective	Outcome	Limitation	Study
Brazilian green propolis	Brazil	80 individuals used propolis. Single-center, open-label, randomized and controlled trial	Verify the effectiveness of Brazilian green propolis (EPP-AF®) as an adjuvant treatment in patients hospitalized with COVID-19.	• Reduction in the hospitalization time. • Possibly, administration early in the disease course would have an even greater benefit in reducing the disease's impact. There was also renal protection in COVID-19 patients. • Propolis can affect various disease mechanisms that are relevant to SARS-CoV-2 infection.	• This trial was open. • The patients were followed for only a short period	Silveira et al. (2021)
NI	Iran	25 individuals used propolis plus *Hyoscyamus niger* L. in randomized and controlled-placebo clinical trial.	Evaluate the effect of a syrup formulation in patients with clinical symptoms of acute respiratory syndrome with suspected COVID-19.	• The results of this study showed that the symptoms of COVID-19 were reduced by the administration of extract of *Hyoscyamus niger* L. plus propolis.	• This study includes the period until the onset of symptoms of the disease is uncontrolled, and the speed of its progression can be variable. • It is uncertain whether the treatment would be effective in hospitalized patients.	Kosari et al. (2021)

NI: Not informed; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019. Source: Authors.

for the binding site of ACE2 and can prevent or delay the entry of SARS-CoV-2 into the cell. Thus, rutin and other flavonoids have prophylactic capacity as inhibitors and competitors of ACE2 (Güler *et al*., 2020).

3.3.5 Interaction of the compound Artepillin C with eukaryotic protein phosphatase 2A (PP2A)

Artepillin C could be a potential drug to exert immunomodulatory activity and reduce the inflammation caused by COVID-19. Maaroufi (2020) analyzed the interactions between PP2A, is involved in the regulation of pro-inflammatory responses during infections by pathogens, of SARS-CoV-2 and the compound artepillin C, which is found exclusively in Brazilian green propolis (Marcucci *et al*., 2001; Park *et al*., 2004). The results of molecular docking demonstrated that artepillin C could compete with the virus to bind to PP2A-B56 (Maaroufi, 2020). This suggests, according to the anti-inflammatory effect of artepillin C, that it could activate, *in vivo*, PP2A-B56 (Maaroufi, 2020).

3.3.6 Interaction of the components and spike protein of SARS-CoV-2

All propolis components had reasonable binding affinity against *spike* protein when compared to avigan, hydroxychloroquine and remdesivir. In addition, rutin had the highest affinity among propolis compounds, suggesting it as a lead compound for further ligand optimization cycle (Refaat *et al*., 2021).

3.3.7 Anti-COVID-19 effects

Elwakil *et al*. (2021) carried out a molecular docking study to predict the binding affinity of compounds from different extracts of Egyptian propolis to RNA-dependent RNA polymerase, spike protein S1 and M^{pro}. Most of the tested fractions had promising binding scores in relation to the reference antiviral drugs (lopinavir and umifenovir). Güler *et al*. (2020) showed that four compounds (pinocembrin, chrysin, CAPE and hesperetin) showed very low binding energies to the ACE2 receptor and the SARS-CoV-2 RBD peak protein. These four flavonoids were also found to have higher affinity than hydroxychloroquine, used as a standard ligand, which was described COVID-19 drug.

Finally, Harisna *et al*. (2021) investigated the molecular interaction of the bioactive compounds of propolis against M^{pro} and the spike protein SARS-CoV-2 by molecular docking. The main compounds with the greatest potential to inhibit M^{pro} from the new coronavirus were methylphiopogonone A, 3'-methoxy daidzein and genistin. As for the spike protein, 4 compounds (neoblavaisoflavone, methylofiopogonone A, 3'-methoxy daidzein and genistin) showed less binding affinity energy than pravastatin (control). However, only neoblavaisoflavone and methylphiopogonone A are able to be absorbed by the gastrointestinal tract.

3.3.8 In vitro evaluation

Güler *et al*. (2021) tested five different concentrations of hesperetin, CAPE and pinocebrine by the ELISA assay. The half maximal inhibitory concentration (IC_{50}) value of commercial propolis was 3 times higher than the sample prepared manually. Hesperetin is the best inhibitor against SARS-CoV-2 spike protein and ACE2 receptor, which has the lowest IC_{50} value (16.88 mmol/L), followed by pinocembrin and CAPE. In addition, pinocembrin had a high affinity by molecular target according to *in silico* studies, while hesperetin was more active in the in vivo study.

Refaat *et al*. (2021) also evaluated the potential for inhibition of M^{pro} by propolis components *in vitro*. The results showed that the propolis extract had a good inhibitory effect against M^{pro} (IC_{50} = 2.452±0.11 µg/mL).

3.3.9 Clinical trials

Silveira *et al*. (2021) conducted a study using standardized propolis extract in hospitalized adult patients with COVID-19. As a result, although not relevant to the need for oxygen supplementation, showed a significant improvement in the clinical status of patients, categorized as a reduction in the length of hospital stay. The group treated with a dose of 800 mg/day showed a median of 6 days (5-11), followed by the group that used a dose of 400 mg/day of 7 days (5-12), compared with the control group with a median of 12 days (8-16) for standard treatment alone. The addition of oral propolis to standard care procedures was safe. No patient had propolis treatment interrupted due to side effects (Silveira *et al*., 2021).

Kosari *et al*. (2021) also evaluated the therapeutic effects of propolis plus *Hyoscyamus niger* L. in patients with acute respiratory syndrome suspected to COVID-19. As a result, after 6 days of intervention, shows a decreasing trend in the clinical symptoms of COVID-19. This finding shows the effectiveness of propolis for the patient's clinical improvement (Kosari *et al*., 2021).

Fiorini *et al*. (2021) showed a case study with improved significantly of patient's general clinical condition, and she recovered, with an negative RT-PCR test result, after consuming three times of a standardized dose of propolis for 12 days in a 52-year-old woman who tested positive for COVID-19 and with mild symptoms.

3.4 Safety of propolis use

Crude propolis is not suitable for human consumption, because it is highly viscous and hydrophobic. However, its 60-80% dilution in ethyl alcohol results in an extract rich in most of its bioactive polyphenols (Ali & Kunugi, 2020; Güler et al., 2020).

Despite the absence of adverse effects in animals and humans, few cases of allergy and contact dermatitis related to the use of propolis were described (Oryan *et al*., 2018). The removal of allergens from propolis may be necessary to avoid possible adverse effects (Aliboni *et al*., 2011). The contact dermatitis with propolis is less frequent in children than adults (Francuzik *et al*., 2019). Reactions may occur due to some allergens, such as 1,1-dimethyl-salicylate, benzyl and benzyl-cinnamate (Pereira & Bártolo, 2016).

This substance has no cytotoxic and genotoxic effect (Cardoso *et al*., 2016; Conti *et al*., 2016; Rocha *et al*., 2013). In addition, these compounds have possible genoprotective effects, reducing damage to DNA in mice (Kumari *et al*., 2017). Fikri *et al*. (2019) showed that a low dose of propolis during the gestation of mice did not alter the fetal development parameters.

Silveira *et al*. (2019) and Fukuda *et al*. (2015) reported that the use of long-term propolis is safe and well tolerated (226.8 mg/day for two months) both by diabetic and non-diabetic patients, reducing proteinuria, lipids, total creatinine and bilirubin (2019). Moreover, there were no changes in the liver, in fasting glycemia and lipids after administration of propolis in patients infected with HIV (Ripari *et al*., 2021).

3.5 Anti-inflammatory property and COVID-19

The activation of PAK1 can cause pulmonary fibrosis (Maruta & He, 2020), which is an aggravating factor in patients with COVID-19. Xu *et al*. (2005) demonstrated that CAPE can inactivate RAC and, consequently, inhibit PAK1. In addition, PAK1 contributes to the suppression of B and T cells, and a normal immune response of patients (Maruta & He, 2020). In addition, several types of flavonoids and prenylated phenylpropanoids, such as baccharin, drupanin and artepillin C, can inactivate PAK1, which the last one is a selectively inhibitor (Messerli *et al*., 2009).

CAPE is a potent inhibitor of NF-kB activation in myelo-monocytic cells (Shimizu *et al*., 2011). Propolis can modulate the function of different cells of the adaptive and innate immune system, such as macrophages, neutrophils, natural killer (NK) cells and lymphocytes, increasing their activity and mechanisms to fight infectious agents (Sforcin, 2007, 2016). Propolis

stimulated the generation of reactive oxygen species (ROS), the expression of toll-like receptor (TLR)-2 and TLR-4, production of pro-inflammatory cytokines and bactericidal and fungicidal activity, suggesting that propolis may activate mechanisms involved in the death of microorganisms (Bachiega *et al*., 2012; Orsatti *et al*., 2010).

In *in vivo* and *in vitro* studies, propolis was able to inhibit the production of interleukin (IL) -17, IL-1β, interferon gamma (IFN-γ), IL-2, IL-6, IL-10 (Okamoto *et al*., 2012; Ripari *et al*., 2021), in addition to increasing the polarization of Th17 to $CD4^{+}Foxp^{3+}$ cells (Piñeros *et al*., 2020). Propolis was able to reduce inflammation, decrease mucus production, the total count of immune, eosinophilic cells and macrophages in bronchoalveolar fluid, IL-5, and the gene expression of IL-13 in the lungs (Piñeros *et al*., 2020). Governa *et al*. (2019) described, in an *in vitro* study against the H1N1 virus, that propolis was able to stimulate pro-inflammatory cytokines (IL-6 and IL-1B).

Moreover, Bufálo *et al*. (2014) demonstrated that propolis was able to exert an immunomodulatory effect on the expression of cell receptors, production of cytokines and fungicidal activity of human monocytes. Propolis modulates the maturation and function of DCS and can be useful in the early stages of the immune response (Conti *et al*., 2016).

Naringin exhibited the highest binding affinity (-9.8 kcal/mol), higher than dexamethasone (-7.9 kcal/mol), a potent anti-inflammatory used to treat patients with COVID-19 in a critical state (Jain *et al*., 2021). Quercetin was superior to kaempferol, myricetin and synthetic indole-chalcone of -7.8 kcal/mol (Vijayakumar *et al*., 2020). In addition, rutin has higher binding affinity than hydroxychloroquine, while all other dissipated compounds with higher binding affinity than Avigan (Refaat *et al*., 2021).

Artepillin C was able to interact via hydrogen bonds, with a higher binding affinity than that of the protein S peptide, suggesting that artepillin C could compete with SARS-CoV-2 to bind to PP2A-B56, and can inhibit acute inflammation associated with COVID-19 (Maaroufi, 2020).

Artepillin C showed inhibitory effect on the binding of LxxlxE-like motifs, which exist in S1 and S2 subunits of S protein, to PP2A-B56 of host cells. Artepillin C can regulate cell function and provide protection against the SARS-CoV-2 induced cytokine storm (Ali & Kunugi, 2021; Maaroufi, 2020). Likewise, the inhibition of deubiquitinating (DUB) activity of papain-like protease (Plpro) by rutin, both *in vitro* as *in silico*, is likely to alter the inflammatory activity of this enzyme (Pitsillou *et al*., 2020).

In summary, propolis and their components have a potent immunomodulatory effect, which can be observed as an inhibitory or stimulatory activity, affecting various cells and components of the immune/inflammatory response, such as adhesion and transmigration of neutrophils, cytokines, chemokines, C-reactive protein, PGE2 and signaling pathways. As propolis is capable of exerting pro and anti-inflammatory activities, it is suggested that clinical trials could be carried out to investigate the effectiveness of propolis and their components in individuals with COVID-19.

3.6 Effect of propolis and their components in the treatment of COVID-19

In silico studies suggest that the use of propolis's flavonoids may be a viable therapeutic option in the treatment of COVID-19 or can be used as lead compounds for ligand optimization. Since they can cleavage of protein S by host cell proteases, for example, TMPRSS2 (Kumar, Dhanjal, Bhargava, et al., 2020), binding of protein spike to cell surface receptors, such as ACE2 (Güler *et al*., 2020; Refaat *et al*., 2021), inhibiting protein spike (Jain *et al*., 2021; Refaat *et al*., 2021) and/or binding of protein spike to the inflammatory in PP2A-B56 (Maaroufi, 2020). In addition to interfering with predicted non-structural proteins (NSPs) of SARS-CoV-2, in order to prevent viral replication (da Silva *et al*., 2020). Therefore, these flavonoids can decrease the chances of the virus entering the host cells and decreasing the viral load, as well as the inflammatory reaction after infection (Ali & Kunugi, 2021).

Kumar *et al*. (2020) observed that the CAPE has affinity to TMPRSS2 involved interactions of hydrogen bonds with two main amino acid residues, in addition to pi-pi interactions with other residues. The inhibitory effect of the propolis compound was better than withaferin, withanone and camostat mesylate, which all had a hydrogen bonding interaction with only one residue.

Luteolin expressed a binding affinity (-10.1 kcal/mol) higher than hydroxychloroquine (-7.7 kcal/mol), camostat mesylate (-9.0 kcal/mol) and remdesivir (-10.0 kcal/mol) (Shawan *et al*., 2021). Another study showed that rutin, CAPE, myricetin, quercetin, pinocembrin and hesperetin expressed a binding affinity for ACE2 higher than the reference molecule (MLN-4760) (Güler *et al*., 2020).

Preliminary results address an inhibitory activity of flavonoids on NSPs of SARS-CoV-2 (da Silva et al., 2020; Hashem, 2020; Refaat et al., 2021). CAPE, chrysin, caffeic acid and galangin bound to NSPs with high binding affinity (Hashem, 2020).

Rutin had a stronger binding affinity with NSPs than hydroxychloroquine (Refaat *et al*., 2021). Likewise, rutin formed stable intramolecular bonds with M^{pro} in a high affinity, comparable to that of teaflavine-3-3 (Shivanika *et al*., 2020). Rutin, comparable to remdesivir, showed the higher affinity with catalytic sites through hydrogen bonds and electrostatic interactions (Arora *et al*., 2020). In addition, it showed higher inhibitory potential to papain-like protease (PLpro) (Pitsillou *et al*., 2021).

Da Silva *et al*. (2020) showed that the affinity of nicotiflorin and rutin binding to protease was close to that of the positive control, while its affinity for RNA-dependent RNA polymerase (RdRp) was better than teaflavine. The binding affinity of rutin metabolites to 3-chymotrypsin like protease (3CLpro) was better than rutin, and its binding to RdRp was also high, while nicotiflorin derivatives expressed the highest binding affinity of all kaempferol glucuronides to RdRp was high. Kaempferol and quercetin were the least potent inhibitors of 3CLpro and RdRp among nicotiflorin and rutin derivatives. Most of the inhibitory effects of all compounds involved hydrogen bonds and pi interactions with 3CLpro and RdRp protein residues (da Silva *et al*., 2020). Vijayakumar *et al*. (2020) showed that several flavonoids and synthetic indole chalcones into the active sites of M^{pro}, quercetin was the second-best inhibitor candidate (-9.2 kcal/mol) following C23 indole-chalcone (-10.4 kcal/mol).

Among the 22 compounds found in Indonesian propolis, broussoflavonol F and glucosperin A had a higher affinity for binding to M^{pro} than the affinity for potent β-coronavirus inhibitors (Sahlan *et al*., 2021). A derivative of podophyllotoxin compounds known as sulabiroin A inhibited M^{pro} through a hydrophobic interaction with His41. In general, flavonoids can inhibit NSPs of SARS-CoV-2 and decrease viral replication (da Silva et al., 2020; Dewi et al., 2021; Hashem, 2020; Pitsillou et al., 2021; Refaat et al., 2021; Sahlan et al., 2021).

In an *in vitro* study, Vero E6 cells were infected with SARS-CoV-2 and treated with naringin. Naringin treatment inhibited SARS-CoV-2 infection and improved the cytopathic effects of the virus compared to control. In addition, naringin exhibited a strong inhibition of human coronavirus replication (Clementi *et al*., 2021). The rutin showed inhibitory activity of PLpro (Pitsillou *et al*., 2021) and DUB activity (Pitsillou *et al*., 2020). Propolis extract and propolis liposome were able to inhibit the enzymatic activity of 3CLpro. Moreover, beyond propolis liposome could be more active than propolis extract, it had an inhibitory effect similar to remdesivir as well (Ali & Kunugi, 2021).

Docking methods can exhibit variability in their ability to reproduce crystallographic pose, indicating that the results on the binding affinity of these methods may not be directly compared (Perola *et al*., 2004). However, similar data were found among the *in silico* studies, suggesting that ellagic acid, p-coumaric acid, CAPE, kaempferol, naringin, luteolin, rutin, quercetin and naringin may be inhibitors of the molecular targets of SARS-CoV-2 (Ali & Kunugi, 2021; Shaldam et al., 2021). Rutin showed the highest potential for inhibition of protein spike, ACE2 and several NSPs of the virus that caused COVID-19 (da Silva et al., 2020; Pitsillou et al., 2021; Refaat et al., 2021).

The effect of rutin was stronger than that of avigan and hydroxychloroquine (Arora *et al*., 2020; Refaat *et al*., 2021). Likewise, the inhibitory effect of luteolin against NSPCs was comparable to camostat mesylate and remdesivir (Shawan *et al*.,

2021). CAPE was able to inhibit TMPRSS2, ACE2 and M^{pro} (Güler *et al*., 2020; Hashem, 2020; Refaat *et al*., 2021), while quercetin inhibited protein S and M^{pro} in an affinity higher than avigan (Refaat *et al*., 2021). Rutin had a considerably higher binding affinity than quercetin against RdRp and M^{pro} of SARS-Cov-2 (da Silva *et al*., 2020). In addition, naringin inhibited spike protein (Jain *et al*., 2021), decreased viral load and cytopathic effects in Vero E6 cells (Ali & Kunugi, 2021; Clementi et al., 2021).

Likewise, clinical trials report early viral elimination, faster symptom recovery and reduced hospital stay in patients with COVID-19 who receive whole propolis extracts (Silveira *et al*., 2021).

Vardhan and Sahoo (2020) in *in silico* study, reported that limonene was the most active compound against the relevant targets (RdRp, ACE2 and peak glycoproteins), but quercetin and kaempferol also obtained high docking scores. Kaempferol can also inhibit TMPRSS2 (Da *et al*., 2019), potentially interacting with ACE2, RdRp and peak glycoprotein. As shown through *in silico* studies, Osés *et al*. (2020) observed a strong inhibition of ACE2 (higher than 90%) of various types of propolis. The best results were with catechin and p-coumaric acid.

3.7 Limitations and prospects

It is important to note that we have included two preprints, which have not been subjected to any form of peer review. In some cases, essential information was missing, such as the nature of the interactions of flavonoids with receptors, amino acid residues and residues involved in the interaction of artepillin C with PP2A, beyond property evaluations of several docking methods. *In vitro, in vivo* and clinical trials are very few and, therefore, more elaborate studies are needed to confirm the efficacy of propolis in patients with COVID-19. It was not possible to perform a meta-analysis of clinical trials because clinical trials are underway.

In general, the methodologies of Structure Based Drug Design (SBDS) are the first tools which have applied into the drug development context. These tools have the principal advantage of decreasing the cost of the process of development as a whole by their practicality and low computational cost (except for molecular dynamics simulations). Thus, these methodologies can search for hits in large data collections of ligands, useful to enrich the high-throughput screening (HTS) campaign, beyond to describe the main forces for intermolecular recognition between molecular targets and ligands. These findings address experimental, semi-synthesis, synthesis total and biological assays studies. On the other hand, as disadvantage, several approximations are applied in the models, beginning with the limitations of molecular mechanics methods, which require an extensive parametrization process. In other words, docking, the principal SBDS method used, is structure dependent, which there is no such tool robust enough to cover all enzymatic diversity. Consequently, evaluation methods have been required to avoid the obtention of false positive results. Finally, propolis has the advantage of natural products, with several bioactive compounds in its composition, requiring further steps of drug development such as ligand optimization.

4. Final Considerations

Brazilian propolis was the only one mentioned in clinical studies that aim and prove the effectiveness of its benefits against COVID-19. Anatolian propolis and Egyptian were tested *in vitro*. In the docking studies, the compounds present in different types of propolis were evaluated, mainly Egyptian and Sulawesi propolis. It was not possible to make a comparison between the types of propolis. Thus, it is suggested that particularities of studies be carried out with the different propolis, both in pre-clinical and clinical studies, in order to evaluate which shows the best results.

In silico studies of the propolis showed potential anti-inflammatory, immunoregulatory and anti-COVID-19 effects, including PAK-1 inhibition. In addition, binding to ACE2, one of the main routes of infection for SARS-CoV-2, can be inhibited by propolis. Propolis compounds, rutin and CAPE specially, demonstrated a strong interaction with ACE2 and TMPRSS2.

In clinical studies, one study demonstrated the effectiveness of propolis in reducing the length of stay in hospitalized patients, while the other showed an improvement in the patient's clinical condition. In addition to these observed effects, there were no reports of adverse events in the clinical studies found.

The return to normal life, but with the risk of contamination by COVID-19, brings the need for drugs that can prevent and treat this disease. In this way, the findings of this systematic review demonstrate that, collectively, there is scientific evidence to confirm that propolis is effective in treating COVID-19. Health professionals should recommend and encourage evidence-based pharmacological treatment. The incentive to health must also follow official guidelines, as well as promote these practices with patients, avoiding self-medication.

The authors suggest that future research involving propolis and its components in COVID-19 be directed towards randomized controlled clinical trials, in addition to comparing the different types of propolis.

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