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Review

Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease
Running title: Propolis against SARS-CoV-2 infection and COVID-19

Andresa Aparecida Berretta [a], Marcelo Augusto Duarte Silveira [b], José Manuel Cóndor Capcha [c], David De Jong [d,*]

[a] Research, Development and Innovation Department, Apis Flora Indl. Coml. Ltda, Ribeirão Preto, São Paulo, Brazil
[b] D'Or Institute for Research and Education (IDOR), Hospital São Rafael, Salvador, Brazil
[c] Interdisciplinary Stem Cell Institute at Miller School of Medicine, University of Miami, Miami, Florida, United States
[d] Genetics Department, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

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ABSTRACT

Propolis, a resinous material produced by honey bees from plant exudates, has long been used in traditional herbal medicine and is widely consumed as a health aid and immune system booster. The COVID-19 pandemic has renewed interest in propolis products worldwide; fortunately, various aspects of the SARS-CoV-2 infection mechanism are potential targets for propolis compounds. SARS-CoV-2 entry into host cells is characterized by viral spike protein interaction with cellular angiotensin-converting enzyme 2 (ACE2) and serine protease TMPRSS2. This mechanism involves PAK1 overexpression, which is a kinase that mediates coronavirus-induced lung inflammation, fibrosis, and immune system suppression. Propolis components have inhibitory effects on the ACE2, TMPRSS2 and PAK1 signaling pathways; in addition, antiviral activity has been proven *in vitro* and *in vivo*. In pre-clinical studies, propolis promoted immunoregulation of pro-inflammatory cytokines, including reduction in IL-6, IL-1 beta and TNF-α. This immunoregulation involves monocytes and macrophages, as well as Jak2/STAT3, NF-kB, and inflammasome pathways, reducing the risk of cytokine storm syndrome, a major mortality factor in advanced COVID-19 disease. Propolis has also shown promise as an aid in the treatment of various of the comorbidities that are particularly dangerous in COVID-19 patients, including respiratory diseases, hypertension, diabetes, and cancer. Standardized propolis products with consistent bioactive properties are now available. Given the current emergency caused by the COVID-19 pandemic and limited therapeutic options, propolis is presented as a promising and relevant therapeutic option that is safe, easy to administrate orally and is readily available as a natural supplement and functional food.

1. Introduction

The COVID-19 pandemic is of grave concern due its impact on human health and on the economy. It is much more deadly than influenza and other types of diseases that recently have had worldwide impact [1], forcing countries to take unusual measures such as limiting travel, closing schools, businesses, and other locations where many people can come into contact with each other. Various public healthcare strategies have been adopted in an attempt to reduce the impact of the disease, but with limited effectiveness, as the virus continues to spread, often through asymptomatic patients [2]. Unfortunately, tests to determine if people are infectious or were previously infected are not widely available, often are costly, and frequently do not provide timely and accurate results. Various therapeutic alternatives have been proposed and tested; however, most require more robust data in clinical trials before they can be widely and safely used [3].

Isolation and stay-at-home measures do not effectively protect essential workers, especially health care personnel, who have become infected and are dying at alarming rates [4]. Economic and other necessities limit how well and how long these isolation measures can be

* Corresponding author.
E-mail addresses: andresa.berretta@apisflora.com.br (A.A. Berretta), marceloadsilveira@gmail.com (M.A.D. Silveira), jmcondor@med.miami.edu (J.M. Cóndor Capcha), ddjong@fmrp.usp.br (D. De Jong).

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maintained, especially in poor countries and in poor communities such as slums and favelas [5,6]. As populations gradually try to get back to normalcy, reducing social distancing, and people in "non-essential professions" return to the workplace, they become more at risk for infection. In this scenario, any options that could help ameliorate disease progression and its consequences, even marginally, would be useful. The world needs safe alternatives to help reduce the impact of this deadly disease.

Natural products, which have historically been widely used to help avoid and alleviate diseases [7–9], are among the options being considered as an adjuvant treatment for SARS-CoV-2 infection [10], because they are generally inexpensive, widely available, and rarely have undesirable side effects. Some have proven antiviral activity [11–13]. An important advantage of using natural remedies is that people who have other health problems or who have mild flu-related symptoms, but do not have the means or courage to visit an already overcrowded medical facility, could take simple and inexpensive measures to help reduce the impact of infection with SARS-CoV-2.

Considering the large number of deaths and other types of damage that the COVID-19 pandemic is causing, there is an urgent need to find treatments that have been approved as safe, and potentially able to inhibit the new coronavirus, reduce its infectivity, and/or alleviate the symptoms of infection [14,15]. Along this line, propolis and its components emerge as potential candidate materials that could help to reduce the pathophysiological consequences of SARS-CoV-2 infection [10].

Infection by SARS-CoV-2, the virus that causes COVID-19, is characterized by binding between viral spike proteins and angiotensin-converting enzyme 2 (ACE2) [16]. Activation of the spike protein is mediated through proteases, such as TMPRSS2, which play important roles in the viral infection [17]. After entry, followed by endocytosis, coronavirus infection causes PAK1 upregulation, a kinase that mediates lung inflammation, lung fibrosis and other critical mortality factors. Increased PAK1 levels also suppress the adaptive immune response, facilitating viral replication [10,18]. SARS-CoV-2 infection is associated with increased levels of chemokines and activated pro-inflammatory cytokines that lead to the development of atypical pneumonia, with rapid respiratory impairment and pulmonary failure [19]. Immunological/inflammatory phenomena (such as cytokine release syndrome) have been shown to be important in the spectrum of SARS-CoV-2 infection. These mechanisms are associated with organ dysfunction more than the viral load *per se* [20]. Along this line, a retrospective observational study found higher serum levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α, in patients with severe COVID-19, compared to individuals with mild disease [21].

There is considerable evidence that propolis can reduce and alleviate the symptoms of inflammatory diseases by affecting various metabolic cycles [22–24]. Recently, several studies have shown that propolis extract and some of its components act against several important targets in the pathophysiological context of the disease caused by SARS-CoV-2, such as reducing TMPRSS2 expression, and reducing ACE2 anchorage, which would otherwise facilitate entry of the virus into the cell; this is in addition to immunomodulation of monocytes / macrophages (reducing production of and eliminating IL-1 beta and IL-6), reduction of the transcription factors NF-KB and JAK2 / STAT3 and blocking PAK1, which determine inflammatory activities and fibrosis caused by COVID-19 [25–28].

Various comorbidities have been associated with severe COVID19 symptoms and a greater chance of patients requiring intensive care; these include hypertension and diabetes. Also, mortality rates of COVID19 patients are much higher in those with cardiovascular disease, chronic respiratory disease, and diabetes [29,30]. There is considerable evidence that these conditions could be alleviated by treatment with propolis. This includes research in animal models of diabetes [31,32], hypertension [33,34], and cardiovascular disease [35,36]. Propolis has properties that are particularly relevant to SARS-CoV-2 infection, such as immune system fortification, reduced viral replication, and anti-inflammatory action [22,24,28,37,38].

2. Propolis and its properties

Propolis is a product derived from resins and plant exudates. Plants defend themselves from pathogens mainly by producing phytochemicals, many of which have been extracted and used in medicine [39]. Plant defense substances collected by bees include phenols and terpenoids [40–42]. Phytochemical compounds that show promise for the inhibition of coronavirus in humans include quercetin, myricetin, and caffeic acid, all components of propolis [43]. Honey bees and many other species of social bees recognize these antimicrobial properties and selectively collect and process these plant products to make propolis, which they use to protect the colony [44]. The production and use of propolis by honey bees evolved to the point that these social bees have considerably fewer immune genes than solitary insect species [45]. Bees in colonies that produce more propolis are healthier and live longer [46], and propolis consumption by the bees augments their immune response to bacterial challenge [47].

The composition of propolis varies according to the plant species available in each region [42,48,49]. As this variability can affect their medicinal properties, standardized propolis products have been developed to help meet the need for a product that does not vary in the main bioactive components and is safe, with minimal interaction with pharmaceutical drugs and proven efficacy in clinical trials [50–53]. In recent decades, it has been shown to have antimicrobial (including antiviral), anti-inflammatory, immunomodulatory, antioxidant, and anticancer properties [54]. Propolis has historically been widely used to alleviate various diseases [7–9,55]; it also has been considered, among other natural alternatives, as an adjuvant treatment for SARS-CoV-2 infection [10], because it is generally inexpensive, widely available and rarely causes undesirable side effects.

Some types of propolis that are highly valued for their medicinal properties, such as Brazilian green propolis, are mainly produced by bees from materials they collect from specific plants, in this case *Baccharis dracunculifolia* [56]. After the botanical origin of the propolis has been identified, extracts of the plant can be made to develop useful products, such as a medicinal mouthwash [57]. However, the medicinal properties of these plant extracts are often inferior compared to the propolis that the bees make from these plant materials [58–60].

3. Why propolis may be a good fit for dealing with COVID-19

Among natural medicine alternatives, propolis has been widely studied and is already extensively consumed in many countries [38,55,61–63]. For example, propolis products, such as throat sprays and extracts, are produced by hundreds of companies in Brazil and are sold as a health aid in nearly every pharmacy throughout the country, demonstrating on a practical basis that they can be safely consumed. These propolis products, and the raw material for their manufacture, are extensively exported by Brazilian companies, especially to Asian countries, including Japan, South Korea, and China [50,64]. The importance of propolis in Chinese, Japanese, Russian and Korean medicine is reflected in the number of patents for propolis containing products registered by 2013, including about 1200 by China and 300 – 400 each for Japan, Russia and Korea [42]. Since 2013, about 1400 new propolis-related patents were applied for in the US patent office. It is a key ingredient in traditional Chinese medicine [65]. Japanese scientists have isolated and patented various Brazilian propolis components for cancer treatment [66], demonstrating their usefulness. In fact, propolis has a wide spectrum of pharmacological properties and is a dietary supplement that is commonly consumed by both healthy and sick people as a preventative precaution and for treatment [67–69]. It is also used in veterinary medicine, due its antibacterial, antifungal, antiviral, antiparasitic, hepatoprotective, and immunomodulatory activities [70].

Table 1
Potential pathways through which propolis and its components could attenuate SARS-CoV-2 infection and its consequences.

N	Targets	Aspect of SARS-CoV-2 infection	Propolis Components	Effect of the components and type of evidence
1	**Viral RNA-dependent RNA polymerase (RdRp) and Spike glycoprotein (SGp)**	Viral component that attaches to host cell	Limonin, Quercetin and Kaempferol	Inhibitory potential with high binding energy to viral components from -9 to -7.1 kcal/mol (*in silico*) [15]
2	**3a Channel Protein**	Viral component that attaches to host cell	Kaempferol	Blocks the 3a channel that is encoded by ORF 3a of SARS-CoV (*in vitro*) [238]
3	**ACE2**	Main receptor for viral entry	Myricetin, Caffeic Acid Phenethyl Ester, Hesperetin and Pinocembrin	Inhibitory potential with high binding energy to ACE2 (-8.97 kcal/mol) (*in silico*) [26]
			Kaempferol	Inhibitory potential with high binding energy to ACE2 (-7.5 kcal/mol) (*in silico*) [239]
			Quercetin	Inhibitory potential with high binding energy to ACE2 (-10.4 kcal/mol) (*in silico*) [25]
3	**TMPRSS2**	Serine protease that mediates spike protein priming for viral entry	Kaempferol	Downregulates androgen receptors such as PSA and TMPRSS2 in a prostate cancer model (*in vitro*) [83]
4	**PAK-1**	PAK-1 (RAC/CDC42-activated kinases) - Responsible for suppression of immune system in hosts	Caffeic Acid and Caffeic Acid Phenethyl Ester	Downregulates PAK-1 associated with Rac1 activation (*in vitro*) [18] Inhibits PAK-1 directly or up-stream, blocking coronaviral infection (Review) [10]
5	**3C-like protease**	Mediates the proteolytic processing of replicase polypeptides 1a and 1ab into functional proteins in SARS-CoV-2 infection	Hesperetin	Inhibits cleavage activity of 3CLpro (*in vitro*) [240]
6	**Inflammatory response**	Response to viral infection that leads to organ injury	Propolis Extract	Inhibits NF-kB activation (*in vitro*) [241] Induces Ca2+ signaling in dendritic cells in Peyer's patches, improving the immune response (*in vitro*) [242] Attenuates the inflammatory response through intracellular ROS and NO levels with downregulation of IL-1β and IL-6 expression (*in vitro*) [27] Regulates IFN-γ, IL-6, and IL-10 cytokines in an experimental asthma model (*in vivo*) [243] Increases TGF-β and IL-10 levels, which contribute to the regulation of the inflammatory process in Acute Pulmonary Inflammation (*in vivo*) [24] Inhibits the production of ROS, RNS, NO, cytokines IL-1α, IL-1β, IL-4, IL-6, IL-12p40, IL-13, TNF-α, G-CSF, GM-CSF, MCP-1, MIP-1α, MIP-1β, and RANTES in stimulated J774A.1 macrophages (*in vitro*) [244]
			Kaempferol	Reduces TNF-α, IL-6, VEGF via the ERK-NFkB-cMyc-p21 pathway (*in vitro*) [83]
			Caffeic Acid Phenethyl Ester	Inhibits NF-kB activation in HTLV-1 infection (*in vitro*) [245] Modulates JAK/STAT signaling and attenuates oxidative stress and inflammation [87].
	Immunomodulation	Adaptive immune response against viral infection	Propolis Extract	Increases humoral and cellular response in mice immunized with Suid herpesvirus type 1[106] Suppresses the differentiation of Th17 cells by inhibition of IL-6-induced phosphorylation of signal transducer and activator of transcription 3 (STAT3) (*in vivo*) [88]
7	**Thrombosis**	Blood clotting dysregulation caused by viral infection	Quercetin	Inhibits thrombin in thrombotic manifestations (*in vitro*) [246]
		Viral translation	Kaempferol and Hesperetin	Inhibits internal ribosomal entry site (IRES) activity required for viral protein translation (*in vitro*) [247]
		Transcription	Kaempferol	Inhibits human immunodeficiency virus reverse transcriptase-associated DNA polymerase as well as RNAase H and RNase H activities (*in vitro*) [248] Presents potent anti-HIV-1 reverse transcriptase activity (*in vitro*) [249]
		Endocytosis		Decreases Akt phosphorylation and viral endocytosis of Rhinovirus (*in vivo*) [250]
8	**Viral replication**	Replication and virion integrity	Quercetin	Prevents up-regulation of diacylglycerol acyltransferase (DGAT) required for hepatitis C virus replication (*in vitro*) [251]
		Replication		Decreases heat shock proteins and Hepatitis B virus transcription levels (*in vitro*) [252]
		Endocytosis		Inhibits Hepatitis B virus-DNA replication (*in vivo* & *in vitro*) [253]
		Endocytosis	Caffeic Acid	Inhibits influenza A virus (IAV) replication (*in vitro*) [254]
		Endocytosis		Inhibits influenza A virus (IAV) activity through neuraminidases (*in vitro*) [255]
		Transcription	Caffeic Acid Phenethyl Ester	Inhibits HIV-1 integrase (Review) [256]

In the wake of the coronavirus outbreak, South Korea has seen a boon in the use of functional foods. According to their Ministry of Food and Drug Safety, "health functional foods" are nutrients that have been proven to be beneficial to health [71]. In March of this year, in response to the coronavirus pandemic, the ministry eased regulations for propolis, which is considered a functional food, and allowed new oral formulations [72]. However, despite considerable evidence that propolis can reduce and alleviate disease symptoms, its acceptance as a health-promoting supplement in human medicine has been limited in many countries such as the USA because of a relevant criticism that propolis products are not standardized and vary in their components and biological activity. In part, this is because propolis varies with the species of plants available in each region, from which the bees collect resins to produce it [42,48,49]. However, standardized propolis products have recently become available to help fill the need for a product that does not vary in the main bioactive components and effectiveness [50,52]. One such option, a standardized Brazilian propolis extract blend [54], has been tested for safety and effectiveness in clinical trials for treating kidney disease and diabetes [51], denture stomatitis [73], and burn patients [74]. Therefore, propolis as a nutraceutical or functional food should be considered as a resource that could help fight against the COVID-19 pandemic.

4. Some propolis compounds can potentially interact with SARS-CoV-2 M^{PRO}

The research community has examined the genetic code of coronavirus and the mechanisms underlying the damages caused by SARS-CoV-2, to help search for drugs and/or potential targets in order to inactive the virus and reduce the damage that it causes. The main protease of coronavirus SARS-CoV-2, M^{PRO} (3-chymotrypsin-like cysteine enzyme), is essential for coronavirus processing of polyproteins and for its life cycle, and therefore inhibition of the active site of this enzyme is a relevant target for drug discovery [75].

Along this line, Hashem evaluated various natural compounds with an *in silico* approach (molecular docking) to try to find useful options for treating SARS-CoV-2 infection. Curiously, caffeic acid phenethyl ester (CAPE), galangin, chrysin and caffeic acid, substances found in several different types of propolis around the world, appeared as potential drugs against this viral target (Table 1) [76]. Specifically, CAPE was predicted to interact with SARS-CoV-2 M^{PRO} in a similar study [77]. Therefore, although it will be necessary to run *in vitro* assays to evaluate the potential anti-SARS-CoV-2 effects of propolis and/or its constituents, these *in silico* results are well boding.

5. Propolis can interact with ACE2 and TMPRSS2, potentially blocking or reducing SARS-CoV-2 invasion of the host cell

SARS-CoV-2 strongly binds to angiotensin-converting enzyme 2 (ACE2), using this enzyme as a receptor for invasion and replication in the host cell [17,78], causing damage and increasing interpersonal transmission [26,79]. Consequently, ACE inhibitors have been considered as useful drug alternatives. However, potential deleterious effects on users of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have emerged as a concern for treatment of COVID-19 patients. An observational study involving 8,910 patients did not confirm this suspicion, and therefore these classes of drugs remain an important tool against potential cardiovascular events [80].

Inhibition of ACE2 enzyme is an important target for treatment against SARS-CoV-2 infection [15,81]. Güler et al. [26] prepared an alcoholic extract of propolis and identified some hydroxycinnamic acids (caffeic acid, p-coumaric acid, t-cinnamic acid and CAPE), the flavanons rutin and myricetin, and the flavones hesperidin, chrysin and pinocembrin. Using molecular docking evaluations, they found that rutin had the highest binding energy to ACE2, followed by myricetin, caffeic acid phenethyl ester, hesperetin and pinocembrin. Rutin interacts with zinc fingers of the active sites of ACE2, a metalloprotease that presents the same zinc finger in ACE [26].

In addition to the *in silico* evidence, Osés et al. [82] evaluated several types of propolis for various characteristics, including inhibition of ACE. They found strong inhibition for most of the propolis types they studied, with higher than 90% ACE inhibition. The best results were found with the propolis components catechin and p-coumaric acid.

ACE2 and TMPRSS2 (transmembrane serine protease 2) on the surface of host cells are used by SARS-CoV-2 via interaction with spike glycoproteins in order to proceed with invasion and replication [15]. Vardhan & Sahoo [15] studied several molecules commonly found in medicinal herbs using molecular docking procedures with relevant targets, such as RNA-dependent RNA polymerase (RdRp), ACE2 and spike glycoproteins and compared the resulting scores with those of hydroxychloroquine [15]. Limonin was the most active compound; however, quercetin and kaempferol, also propolis compounds, gave high docking scores [15]. Kaempferol was studied in prostate cancer models, and the expression of TMPRSS2 was reduced, showing a potential mechanism of action for an antitumoral effect [83]. Kaempferol could be an important propolis component for use against COVID-19, since it is involved in the inhibition of TMPRSS2 [83], potentially interacting with ACE2, RdRp and spike glycoprotein (SGp) [15], besides its antiviral activity [84] (Table 1).

6. Propolis blocks PAK-1, potentially avoiding lung fibrosis and restoring a normal immune response

Among the possible targets for controlling COVID-19 damage, the major "pathogenic" kinase PAK1 is key. It is an essential component in malaria and viral infections, but it is also involved in a wide variety of other diseases and disease conditions, including cancer, inflammation, and immuno-suppression, when abnormally activated. Consequences of PAK1 activation include lung fibrosis [10], which is an aggravating factor in COVID-19. PAK1 is activated by RAC. Xu et al. [18] demonstrated that caffeic acid and its ester (CAPE), components of propolis, can inactivate RAC, consequently inhibiting PAK1. The inactivation of PAK1 directly, or up-stream, can potentially attenuate coronavirus pathogenesis [10]. B-cells and T-cells are lymphocytes that produce specific antibodies against viruses and other intruders, and PAK1 contributes to their suppression. PAK1 inhibitors can both help combat the virus and restore a normal immune response [10].

Propolis from Europe and temperate Asia, usually made by bees from resins collected from Poplar trees, has predominantly flavonoid compounds, while green propolis (from *Baccharis dracunculifolia*), a propolis exclusively found in Brazil, has various kinds of flavonoids and prenylated phenylpropanoids, such as artepellin C, baccharin and drupanin. These and all other types of propolis can inactivate PAK1 [10]. Artepillin C selectively inhibits PAK1 [85] (Table 1).

Some studies have shown that propolis can act as an immunostimulant, with the ability to improve the immune response. Its components increase neutralizing antibody titers, activate phagocytosis, and increase IFN-γ levels and the number of lymphocytes [86]. An increase in IFN-γ levels was also detected by Shimizu et al. [28], who evaluated the mechanisms involved in the effects of some types of propolis in a herpes simplex animal model.

CAPE (caffeic acid phenethyl ester) is a potent inhibitor of activation of NF-kB in myelo-monocytic cells. Ansorge et al. [37] demonstrated that propolis, CAPE, quercetin, hesperidin and some other propolis flavonoids can inhibit the cytokine production of Th1 and Th2 type T cells, while increasing TGF-beta 1, an important anti-inflammatory cytokine. Moreover, CAPE can attenuate oxidative stress and inflammation through down-regulation of JAK2/STAT3 signaling [87] as well as having an immunomodulatory effect, in which CAPE inhibits IL-6 phosphorylation and STAT3, which are important for pro-inflammatory Th17 development [88].

Besides the anti-inflammatory effect of CAPE and kaempferol,

Paulino et al. [89] evaluated the anti-inflammatory effect of artepellin C in rat paw edema and in cell cultures, demonstrating that the activity was at least in part mediated by prostaglandin E2 and NO inhibition through NF-kB modulation. Artepillin C is an important biomarker of Brazilian green propolis (botanical source *Baccharis dracunculifolia*).

Immune modulation is desirable since coronavirus infection dysregulates the immune response in the initial phases of infection, which facilitates viral replication. However, in later stages of COVID-19, the body develops an exaggerated inflammatory response, which can greatly damage the lungs and other organs. Propolis, different from typical immunosuppressants, can help avoid immunosuppression during the initial phases of disease and, in later stages, reduce an exaggerated host inflammatory response, inhibiting excess IL-6, IL-2 and JAK signaling [90]. CAPE, a propolis component, is also known as an immune-modulating agent [91] and should be considered as an alternative to help reduce an exaggerated inflammatory response. In a mouse model, propolis had immunomodulatory action *in vivo* on Toll-like receptor expression and on pro-inflammatory cytokine production [92].

There is ample evidence for interference of propolis and/or its components with viral replication and infectivity, potentially decreasing lung inflammation due to anti-inflammatory properties, while promoting immune system fortification. These are useful properties that could help minimize the symptoms and deleterious effects of COVID-19 (Fig. 1).

7. Propolis as an antiviral substance

Propolis has been tested against various viral disease organisms; initial successes have prompted research to determine the most useful components, which may be modified to produce more active and specific pharmaceuticals [93]. Viruses that were controlled by propolis in animal models with suggestion for control in humans include influenza [11,94], herpes simplex virus type 2 [95], and HIV [93,96]. Shimizu et al. [28] evaluated three different types of propolis in ethanol extracts, using a murine model of herpes simplex virus type 1. Despite the chemical differences due to the different plant origins of the resins the bees used to produce the propolis (*Baccharis dracunculifolia*, *Baccharis eriodata* and *Myrceugenia euosma)*, all three propolis extracts not only had direct anti-HSV-1 effects, but also stimulated immunological activity against intradermal HSV-1 infection in mice.

Antiviral activity of propolis has been reported for DNA and RNA viruses (poliovirus, herpes simplex virus, and adenovirus) in an *in vitro* model (cultured cells). The best results were obtained against poliovirus and herpes virus, with 99.9% inhibition of the latter, at a propolis concentration of 30 ug/ml [97]. The propolis components chrysine and kaempferol caused a concentration-dependent reduction of intracellular replication of herpes-virus strains when host cell monolayers were infected and subsequently cultured in a drug-containing medium. Quercetin, another propolis component, had the same effect, but only at the highest concentrations tested (60 ug/mL) against various human herpes simplex virus strains, with a intracellular replication reduction of approximately 65%, while it reduced the infectivity of bovine herpes virus, human adenovirus, human coronavirus, and bovine coronavirus about 50%. The reduction was 70% in the case of rotavirus [84].

8. Anti-inflammatory and immunomodulatory properties of propolis

The most critical cases of COVID-19, which require ventilator-assisted intensive care and often result in prolonged ventilator dependency and death, are a result of an exaggerated inflammatory response to infection [98]. SARS-CoV-2 infection is associated with increased levels of chemokines and activated pro-inflammatory cytokines that lead to the development of atypical pneumonia, with rapid respiratory impairment and pulmonary failure [19]. Immunological/inflammatory phenomena (such as cytokine release syndrome) have been shown to be important mortality factors in SARS-CoV-2 infection. Higher serum levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α, are found in patients with severe COVID-19 compared to those of individuals with mild disease [21]. Molecular mechanisms involved in this immune process are the targets of various synthetic medicines being tested in patients, including ciclesonide, hydroxy chloroquine, ivermectin, and ketorolac, which are PAK1 blockers [10]. PAK1 (RAC/CDC42-activated kinase 1) is overexpressed in the lung in response to SARS-CoV-2 infection and is a critical mediator of the cytokine storm that frequently results in mortality in hospitalized patients [99]. Fortuitously, propolis components are effective PAK1 blockers (Table 1).

There is considerable evidence that propolis can reduce and alleviate the symptoms of inflammatory diseases [22–24] and has immunomodulatory properties [24,37]. However, these properties can vary according to the plant origin of the propolis, as well as the extraction process/solvent used and the inflammatory protocol (cell culture, animal models, induction by lipopolysaccharides) when the propolis extracts are tested [50]. Tests with animal models have shown that propolis can reduce the levels of IL-6 and TNF-alpha, which are key pro-inflammatory mediators, and increase the levels of the regulatory cytokine IL-10 [24]. Kaempferol, a propolis component, reduces IL-6, TNF-alpha, and VEGF (vascular endothelial growth factor) via the ERK-NFkB-cMyc-p21 pathway [83] (Table 1).

Tests on macrophage cell cultures also demonstrated that propolis inhibits the production of IL-1 beta, an important component of the inflammasome inflammatory pathway, in diseases such as rheumatoid arthritis, lupus and other autoimmune diseases [55]. Although the mechanisms of action are not well elucidated, these propolis components have potential as complementary supplements in the preventive treatment of chronic inflammatory diseases [100].

9. Propolis has potential as a vaccine adjuvant

Propolis is considered a safe immunostimulant and a potent vaccine adjuvant [101]. Propolis has been widely tested as a vaccine adjuvant, because it induces an earlier immune response and provides a longer protection period [102]. It is also included as an adjuvant ingredient in traditional Chinese medicine [103]. Propolis flavonoids have potential as adjuvants, enhancing IgG, IL-4, and IFN-γ in serum [104]. Fernandes et al. [86] found that propolis exerted a positive adjuvant effect on vaccines that were developed against canine coronavirus. They assayed IFN-γ, which is an effective way to measure the cellular response induced by a vaccine. In a mouse model, propolis, added as an adjuvant to inactivated swine herpesvirus type 1 vaccine, stimulated increased cellular and humoral responses, increasing IFN-γ [105,106]. Propolis enhanced the immune response to inactivated porcine parvovirus vaccine in guinea pigs [107]. When added to a Trichomonas vaginalis protein vaccine, propolis increased the IgG antibody response 4-10 times in mice, compared to the protein alone [108]. Propolis was also effective as an adjuvant in the immunization of cattle with bovine herpesvirus [105]. It improved the humoral and cellular responses in mice inoculated with inactivated virus vaccines [109]. Propolis as an adjuvant gave a similar immune response (increasing IFN-γ levels), to Alum and Freund's adjuvant in mice vaccinated with an HIV-1 polytope vaccine candidate, with less risk of undesirable side effects [110].

10. Comorbidities and evidence of how propolis can help reduce their impact in COVID-19 patients

10.1. Cancer

Cancer is considered a relevant comorbidity factor for COVID-19. Cancer patients have a 3-4 times higher risk of progressing to severe COVID-19 disease than patients without comorbidities. Also, the hospital environment during the coronavirus pandemic can interfere with

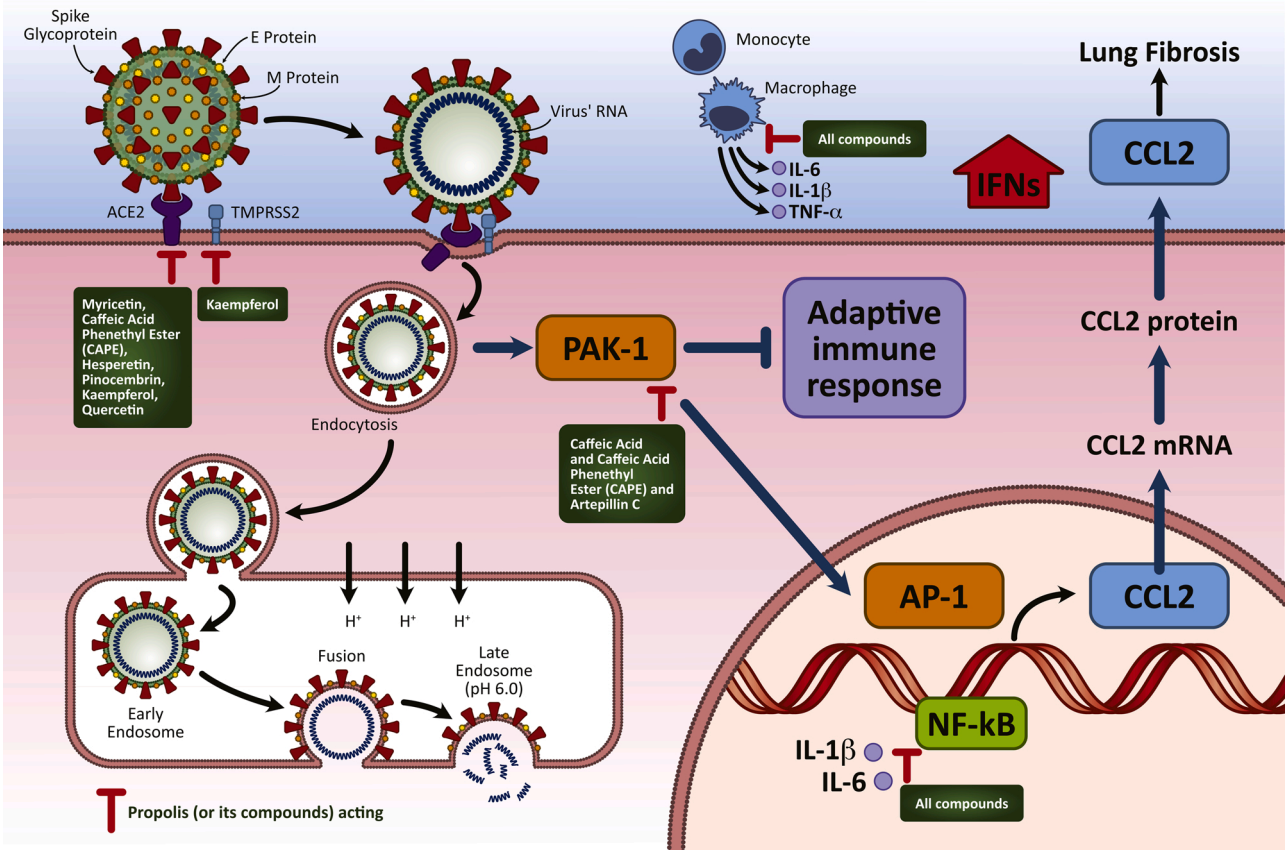

Fig. 1. Major pathways through which propolis can interfere with SARS-CoV-2 attachment to the host cell, viral replication, and pathophysiological consequences. SARS-CoV-2 entry into target cells requires spike protein binding to ACE2 and activation by TMPRSS2. After binding, several signals are triggered, allowing viral endocytosis and PAK1 activation, which reduces the adaptive immune response and antibody production against the virus. PAK1 also stimulates CCL2 production, which generates a fibrotic response. Viral infection induces nuclear transition factor NF-KB activation, generating local pro-inflammatory cytokine production. Propolis-derived compounds downregulate the expression of TMPRSS2 and the anchoring ACE2, which limits entry of the virus. Furthermore, they promote NF-KB and monocyte/macrophage immunomodulation, reducing pro-inflammatory cytokine overproduction, and they reduce PAK1 activation, increasing the production of antibodies against SARS-CoV-2.

or delay the treatment that cancer patients should receive. Patients with symptoms may choose not to risk a visit to a clinic or hospital to determine if they have cancer [111]. Alternative therapies could help retard cancer or reduce the impact of cancer and cancer treatment in COVID-19 patients.

Propolis has potential as a complementary therapy for cancer. It has shown efficacy against various types, including bladder, blood, brain, breast, colon, head and neck, kidney, liver, pancreas, prostate, and skin cancers [112]. Propolis could help prevent cancer progression; in various parts of the world it is considered an alternative therapy for cancer treatment [113]. Propolis extracts have been found to inhibit tumor cell growth both *in vitro* and *in vivo*, including inhibition of angiogenesis, demonstrating potential for the development of new anticancer drugs [114–116]. Various components of propolis have been shown to inhibit cancer cell growth, including cinnamic acid [66], CAPE [117–119], quercetin [120], and chrysin [121]. Propolis and its components normally have little impact on normal cells, displaying differential cytotoxicity in liver cancer, melanoma and breast cell carcinoma cell lines [122,123]. Propolis enhances the activity of tumor necrosis factor related apoptosis inducing ligand (TRAIL) in cancer cells [124].

10.2. Hypertension and cardiovascular disease

Hypertension and cardiovascular disease are considered relevant comorbidities for COVID-19 [125–127]. Propolis has demonstrated anti-hypertensive effects in rat models [33,34,128,129]. In Cameroon, it is used in popular medicine to treat various ailments, including high blood pressure [130]. Propolis has been widely used as a dietary supplement for its health benefits, including cardiovascular protective effects [131,132]. In a human trial, consumption of propolis improved critical blood parameters, including HDL, GSH and TBARS levels, demonstrating that it could contribute to a reduced risk for cardiovascular disease [132].

10.3. Obesity

Obesity is a major comorbidity and predictor of increased mortality in COVD-19 patients. Obesity and SARS-CoV-2 both induce an inflammatory process, exacerbating SARS-CoV-2 infection in the obese [133]. Propolis reduced inflammation and prevented hyperlipidemia and metabolic syndromes in highly caloric diet induced obesity in mice. Body weight gain, visceral adipose tissue, liver and serum triglycerides, cholesterol, and non-esterified fatty acids were all reduced in the propolis fed mice [78,134]. Caffeic acid phenethyl ester, a propolis component, is a natural anti-obesity agent [135].

10.4. Thromboembolism, thrombosis and microthrombosis

Microthrombosis, disseminated intravascular coagulation, and consequent multiorgan failure are common in severely affected COVID19 patients, with associated high mortality rates [136–139]. Anticoagulants are sometimes prescribed to such patients because they

can reduce mortality (Tang et al. 2020). An elevated level of plasminogen activator inhibitor-1 (PAI-1) is a biomarker and risk factor for thrombosis and atherosclerosis [140,141]. Various types of evidence demonstrate that propolis can reduce platelet aggregation and other thrombosis-related parameters. Propolis decreased thrombotic tendencies in mice by suppressing lipopolysaccharide-induced increases in PAI-1 levels [142,143]. Propolis downregulated platelet-derived growth factor and platelet endothelial cell adhesion molecules in low-density lipoprotein knockout mice [144]. Platelet aggregation was reduced by propolis in tests on human blood *in vitro* [145] and in other *in vitro* tests [146]. Caffeic acid phenethyl ester (CAPE), a well-studied bioactive propolis component, inhibits collagen induced platelet activation [147].

10.5. Old age

The elderly are more often affected by chronic inflammation, characterized by systemically increased levels of proinflammatory cytokines, which can contribute to development of a cytokine storm, a major cause of COVID-19 mortality [148]. Propolis has antioxidant properties, which could help retard or reduce aging processes [149]. CAPE, a propolis component, increased the lifespan of *Caenorhabditis elegans*, a common model organism for aging studies [150]. Propolis consumption protected against cognitive decline in elderly subjects (humans) exposed to high altitudes [151]. Serum TGF-β1 and IL-10 levels were significantly higher in propolis-treated elderly subjects, helping reduce inflammation, which could be the mechanism of protection against cognitive decline. Activity of superoxide dismutase (SOD), a key antioxidant in men treated with propolis was increased, while malondialdehyde, a marker of oxidative stress, decreased [152]. The same tendencies were detected in a diabetic rat model [153]. Propolis has the potential to reduce neurodegenerative damage through antioxidant activity, which helps protect against cognitive impairment in Alzheimer's disease as well as aging [154,155]. In a mouse model of Alzheimer's disease, coniferaldehyde, an active ingredient in propolis, had neuroprotective effects. It reduced brain β-amyloid deposits and pathological changes in the brain, helping preserve learning and memory capacity [156]. The angiotensin system, which is key to SARS-CoV-2 invasion of host cells, is associated with senescence. One of the reasons that SARS-CoV-2 causes significantly higher mortality in older patients may be that they have a larger number of senescent lung cells, which are a vulnerable target for viral infection and can help promote viral replication. That would make senolytic drugs useful to help the elderly survive COVID-19. Quercetin, a propolis component, which has been proposed as a therapeutic for treatment of COVID-19, has senolytic activity [157].

10.6. Diabetes

Common comorbidities with high death rates in critically ill COVID19 patients include diabetes [30]. Given the relation between diabetes and inflammation, and that flavonoids, major bioactive components of propolis, protect against free radicals and other pro-oxidative compounds, it is plausible that propolis consumption can reduce the risk of diabetes [158]. Brazilian propolis has become popular as a healthy dietary supplement in various parts of the world because it can help prevent inflammation and diabetes [159]. Propolis was found to reduce blood glucose, blood lipids and free radicals in diabetic rats [31,160]. It also reduced glycemia [32,161] and insulin resistance [162–164] in diabetic rats. Experimental diabetic nephropathy was also prevented [165]. Diabetes symptoms were reduced in a diabetic mouse model [166], apparently by attenuating immune activation in adipose tissues.

Clinical trials with diabetic patients demonstrated that propolis consumption improved antioxidant parameters [167], glycemic control [168,169], and the lipid profile and renal function [170]. Propolis is also an antimicrobial agent with wound healing properties [171,172], which has proven especially useful for diabetic patients [173,174], who tend to develop difficult to heal wounds.

Caffeic acid phenethyl ester (CAPE) is considered an anti-obesity agent with beneficial effects on inflammation and diabetes [175]. CAPE reduced insulin resistance in diabetic mice and in hepatic cell culture [176]. Chrysin, another component of propolis, also has anti-diabetic properties [177].

10.7. Kidney diseases

COVID-19 is an important threat for patients with comorbidities such as renal or hepatic impairment [178]. The kidney is a common target of SARS-CoV-2 [179]. COVID-19 patients are at increased risk of kidney impairment [79], and consequently many patients with COVID-19 present renal dysfunction [180]. Increased mortality is common in COVID-19 patients with chronic kidney disease and in those undergoing hemodialysis [181]. Propolis has shown protective effects against kidney diseases. Nephropathy was prevented by propolis treatment in animal models [165,182,183]. Brazilian red propolis attenuated hypertension and renal damage in a rat renal ablation model [184]. Anti-diabetic activity of propolis in a rat model reduced liver damage [160]. In a pioneering clinical trial, propolis reduced proteinuria in patients with chronic kidney disease [51].

10.8. Bacterial infection

Bacterial infection is a common complication in COVID-19 [79]. Propolis has a long history of use for its antibacterial properties and could help treat bacterial infections in COVID-19 patients. The healing properties of propolis are referred to throughout the Old Testament, and propolis was prescribed by Hippocrates in Ancient Greece for the treatment of sores and ulcers [185]. Propolis has been popular for centuries in Russia and other countries in Eastern Europe for its antibacterial properties [186]. The pharmacological value of propolis comes from a natural mixture of antibacterial substances, instead of only one or a few substances as in most medicines [187]. Propolis components galangin, pinocembrin, rutin, quercetin, and naringenin, as well as CAPE increase bacterial membrane permeability, which could explain their antimicrobial properties [188]. De Campos et al. [189] showed that the main mechanism of action of propolis is rupture and lysis of bacterial cells. Propolis has demonstrated antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *E. coli* [190], including methicillin-resistant and methicillin-susceptible strains of *Staphylococcus aureus* [191]. Adding propolis extract to the antibiotics, ampicillin, gentamycin and streptomycin, vancomycin and oxacillin increased their antibacterial activity against *Staphylococcus aureus* [192,193]. The extract also reduced cell adhesion and consequent biofilm formation by this bacterium [193]. Propolis (sometimes known as bee glue) has antibacterial activity against human tubercle bacillus, but often has only limited activity against Gram-negative bacilli. These antimicrobial properties appear to be due to its high flavonoid content [186]. Propolis can help avoid bacterial tooth decay [194]. Propolis and some of its components inhibit bacterial motility [195]. Black poplar, *Populus nigra*, tree resin is the main source of the propolis used for medicinal purposes in Europe; it contains phenols and flavonoids that have well known antimicrobial properties [196]. Propolis can be bacteriostatic and or bactericidal, depending on the concentration [197]. An ethanol extract of propolis inhibited microbial growth and biofilm formation by *Pseudomonasaeruginosa* [198]. The antibacterial properties of propolis make it a useful ingredient in a wound healing biofilm [199].

11. Limitations: Lack of standardization

Man has used propolis as an herbal medicine for thousands of years. Various useful activities have been described for propolis, including, and not limited to antiviral, antibacterial, antifungal, anti-inflammatory, immunoregulatory, antioxidant, and wound healing properties [200,201]. However, plant geographical source, bee species, seasonality and

climatic differences can dramatically affect chemical composition [48,202]. These details, along with variations in the processing and solvent extraction processes (which can selectivity extract some compounds according to their polarity) [203], can influence its biological properties. This can affect and limit the repeatability of tests and confuse the compilation of results used to determine appropriate dosages for human clinical trials, ultimately causing insecurity for prescribers.

Considerable work has gone into understanding the mechanisms involved in the biological properties of propolis [54,189,204,205]. Also, efforts have been made to improve technological and analytical processes to determine adequate extraction procedures that preserve its bioactive compounds and consistently provide the best pharmacological properties for each medical condition [50,200,201,203,206–208]. However, although propolis is a product that can be offered to the market in several presentations and with different classifications according to the type of product, possibly as a health supplement, food supplement, cosmetic and/or hygiene product, the various beneficial effects that appear in published research were not accepted by the European Commission as acceptable "claims", based on the argument that there are qualitative and quantitative variations in the bioactive flavonoids, which are dependent on the raw material provided by beekeepers. Those factors, and the lack of standardized extraction and preparation methods, are reasons that do not permit this type of approval [209], justifying the standardization proposed by Chan [38].

Although in the bee products field “standardization” is not yet a normal procedure, this reality already exists in the phytopharmaceutical industry. When working with herbal products, it is normal to find differences in the raw material received, since plants suffer a strong influence of the environment, including seasonality, soil treatment, other plant species nearby, and various other conditions, resulting in batches of plant materials that are often chemically different, qualitatively and/or quantitatively. It is not possible to have identical batches when working with this type of material; however, minimal standardization is needed in order to validate safety and efficacy studies and guarantee useful characteristics when a product is offered to the market [210].

The definition of “Standardization” by the American Herbal Product association is: *“Standardization refers to the body of information and control necessary to produce material of reasonable consistency*” [211]. The mechanisms and technologies available to meet this goal are available; however, challenges also exist. Nikam et al. [210] present useful guidelines for those who intend to develop such standardization.

11.1. A Standardized Propolis Product

In Brazil, 12 main types of propolis have already been described [201]. Due to this great variability and the limitations that these differences cause in the research, development and industrial fields, Berretta et al. [54] developed a Standardized Propolis Extract, named EPP-AF® (Patent Letter no. 0405483-0, approved by Industrial Property Magazine on July 23, 2019), which possesses reproducibility batch-to-batch for a group of phenolic and flavonoid compounds, in addition to a characteristic HPLC *fingerprint* and consistent biological effects (antimicrobial activity) [54]. Several studies have been conducted with this extract, including analytical development and validation [54,212,213], biological effects such as antimicrobial, antifungal and wound healing properties [54,205,214–217], and anti-inflammatory and immunoregulatory activities [22,24].

12. Safety and Efficacy Studies

12.1. Non-Clinical Studies

Besides the long history of traditional use of propolis for treating diseases, various studies in animals have demonstrated the safety of propolis [218–220]. Safety studies for EPP-AF® have been conducted using an *in vitro* Ames Test, demonstrating a lack of abnormalities in the bacterial strains that were evaluated (unpublished data) and a lack of abnormalities in a micronucleus test (*in vitro*) [221]. Tavares et al. [222] also studied propolis using a micronucleus tool, with the mutagenicity agent doxorubicin as a positive control. They found that the propolis behaved as a “Janus” compound; it was genotoxic at higher concentrations and chemopreventive at lower ones. This demonstrates the importance of the appropriate dosage and model for testing, which are needed to correctly extrapolate to clinical trials. Additionally, acute and subchronic animal toxicity tests were performed; even at very high treatment levels, EPP-AF® propolis did not reach an LD_{50} dose (maximum tested 3000 mg/kg) [223]. The safety data from tests with Wistar rats (1000 mg/kg) and rabbits (300 mg/kg), and the conversion factor proposed by the US Food and Drug Agency were used to propose the dosages for human trials [50]

12.2. Clinical Trials

A clinical safety study was carried out at the Ribeirão Preto School of Medicine of the University of São Paulo (FMRP/USP) with healthy volunteers in order to assess the safety of ingesting 375 mg / day of Standardized Propolis Extract (EPP-AF®), for five days. No adverse events were observed. The study pointed to the absence of acute toxicity after the oral use of Standardized Propolis Extract (EPP-AF®) at a dose of 375 mg daily for five days. The significant positive variation observed in the parameter HDL cholesterol needs further studies with a larger number of patients to confirm this beneficial effect on the cardiovascular system (unpublished data).

In addition, and more important in this case, a study to evaluate drug interaction was performed using a *cocktail* approach to analyze the main hepatic metabolizing enzymes (cytochrome P450 enzymes - CYPs) and the transport enzyme Pgp. The results showed that this standardized propolis extract is safe and without risk of drug interaction, according to the criteria established by the WHO [53]. The propolis tested in the interaction study was provided in tablets; consequently, these results cannot necessarily be extrapolated to a propolis alcohol extract.

Using a propolis preparation, a clinical trial that was randomized, double-blind, and placebo-controlled was conducted with 430 children (1-5 years old) in Israel with a placebo elixir and Chizukit (a standard over-the counter drug containing Echinacea extract 50 mg/ml (*Echinacea purpurea* and *E. angustifolia*), 50 mg/ml of propolis extract and 10 mg/ml of vitamin C, for respiratory tract infection gave good results [224]. Another clinical study was done for asthma treatment in adults [204]. The study, which used a propolis water extract, demonstrated reduction in key pro-inflammatory cytokines, including tumor necrosis factor (TNF-a), ICAM-1, IL-6, IL-8 and a 3-fold increase in the “protective” cytokine IL-10; the levels of prostaglandins E2, F2a and leukotriene D4 were reduced significantly [204].

A randomized double-blind placebo controlled clinical study of 32 patients with Chronic Kidney Disease, demonstrated safety of the Standardized Propolis Extract (EPP-AF®) at an oral dose of 500 mg / day after administration during 12 months, with significant reduction in proteinuria and urinary MCP1 in the propolis group compared to the placebo [51], with no side effects. Another clinical study conducted with the Standardized Propolis Extract (EPP-AF®) in healthy volunteers aimed to assess the antioxidant activity. There was a reduction in cell damage induced by oxidative stress in healthy volunteers, due to an increase in the enzymatic antioxidant capacity, especially affecting superoxide dismutase (SOD), and decreasing lipid peroxidation and DNA oxidation (8-OHDG) (article submitted). These data indicate the important protective effect that propolis has on cells, tissues and on the human body, reducing the effects of aging, degenerative diseases and several other conditions that involve these oxidation processes.

Another relevant clinical trial was conducted by Soroy et al. [225] on dengue hemorrhagic fever patients. Their double-blind, randomized and placebo-controlled trial evaluated the propolis product Propoelix™ (two 200 mg capsules, three times a day), demonstrating an

improvement in platelet counts and a decrease in TNF-alfa, promoting a reduction in the duration of hospitalization time of the patients.

The current COVID-19 pandemic has promoted strong interest in propolis as a therapeutic option. As a consequence, a clinical trial of Brazilian green propolis extract (EPP-AF) for treatment of COVID-19 patients was recently initiated in Brazil (https://clinicaltrials.gov/ct2/show/NCT04480593).

12.3. Dosages

Clinical trials with propolis have been conducted in various regions of the world, most of them with the limitation of a lack of standardization. Berretta et al. [50,51,53] evaluated many of them; the most common dosage used was 500 mg/day for adults. Considering the case of EPP-AF®, the clinical data until now support dosages of 375 - 500 mg of propolis/day; however, non-clinical trials indicate that much higher dosages can be tolerated and may be useful [211]. The dose of 500 mg/day would be equivalent to 30 drops of propolis extract (with 11% w/v of dry matter), 3 to 4 times a day, diluted in about 100 ml of water, or 3 to 4 units/day of capsules or tablets with the equivalent amount of extract. For preventive purposes, 30 drops/day or one capsule, are usually taken. However, considering the dosage safely used by Soroy et al. [225] of 1200 mg/day, in more severe cases of COVID-19, dosages higher than 500 mg/day could be useful.

13. Supplements, Food and Hygiene Products made with Propolis

Propolis extracts and sprays, often combined with medicinal herb extracts and honey, are now found in nearly every pharmacy in Brazil, attesting to their safety, popularity and usefulness in this country, where hundreds of companies currently produce these “natural medicines”. For each regulatory category and country, the technical rules to be followed for propolis products vary. Some countries such as Brazil, Canada, United States of America, China, South Korea, Japan, Australia and the European Community already possess regulation for propolis [50]; consequently, propolis can be easily found by consumers at a low cost and potentially can be useful for preventive and/or curative purposes in the early stages of disease.

14. Why consider using nutraceuticals or other natural alternatives instead of relying on modern pharmaceuticals?

Propolis is extensively used in foods and beverages because of its benefits for human health. It contains hundreds of natural compounds, including aldehydes, coumarins, polyphenols, steroids and inorganic compounds, with a broad spectrum of biological and pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, antitumor, anticancer, antiulcer, hepatoprotective, cardioprotective, and neuroprotective actions [226]. The health industry has always used natural products, including propolis, as an alternative source of drugs [62]. The complex mix of propolis components can provide greater health benefits than would be apparent by analyzing the individual effects of components, apparently due to synergistic effects [97].

Modern medicine relies on powerful drugs that have specific and strong impacts on disease organisms and on the body. This strategy and adequate sanitary measures have proven to be highly effective, resulting in an almost constant increase in human lifespan, which has more than doubled since 1900 to over 70 years [227]. However, the system in place for approving pharmaceuticals also has some disadvantages, including the long lead time and considerable funding needed to discover new options, test them for safety and effectiveness, and after 5-10 years, obtain approval for their use. Due to the high costs involved and the possibility that this extended process will not result in a product that will compensate the investment required, potentially useful materials may never become available. Another problem is that modern medicine can be quite expensive, with constantly increasing costs for individuals and countries. Consequently, adequate healthcare may not be available to everyone who needs it. Side effects of many of these powerful medicines are also a concern. Doctors and patients often need to weigh the risk of drug side effects against the consequences of the disease. Also, for some diseases no effective drug is available and patient care focuses on relieving symptoms and the consequences of infection.

Among alternatives to modern drugs, there has long been a traditional use of natural health products. However, such products normally cannot be registered as medicines; the considerable investment needed to qualify them as such often would not be compensated because they are difficult to obtain a patent for and people could easily purchase or collect them. Curiously, one of the strategies for developing modern drugs is to carefully dissect the components of natural products, determine which ones have desirable activity, patent and synthesize them and then go through the expensive process of getting them approved, though with some possibility that such products could give a return on the investment because of the patents. A case in point is Brazilian green propolis, for which there is considerable evidence of anticancer properties [228,229]. This propolis is not patented, but some if its components were isolated, and synthesized, and are now patented drugs for cancer treatment [230]. Brazil continues to produce and export large quantities of green propolis, especially to Asian countries, but various patented components are the property of companies in other countries.

In some parts of the world, the equivalent of the US Food and Drug Administration (FDA), officially classifies certain natural products as “Functional Foods” or some other similar category. As such, they can be produced and marketed and used by people who believe they will be good for their health. To be classified as functional foods, these agencies require proof that they are safe and that they have proven health benefits [71,231]. This option provides alternatives that are normally inexpensive and do not require prescriptions. Specifically, propolis has been suggested as a prophylactic treatment for high risk groups in the current COVID-19 pandemic [232].

Some investment is necessary to help qualify and register natural medicines, which may be provided by companies or by government programs that recognize the need for this type of investment, or both. In Brazil, the Sao Paulo state research agency (FAPESP), has a program called PIPE (http://www.fapesp.br/pipe/) that helps small companies finance this type of research for products that they recognize would not normally be developed without this type of support, including natural pest control alternatives for agriculture and “natural medicine” formulations. Various research projects on propolis products have been financed by this FAPESP PIPE program including wound healing and antifungal products [54,205,214–216], and the development of a standardized propolis formulation [54]; tests of this product were made for safety and effectiveness in patients with chronic kidney disease and diabetes [51]; both diseases are the subjects of projects supported by FINEP (Brazilian Study and Projects Financing Agency).

While modern medicines normally have only one or just a few active components, natural products can have many. Propolis, for example, has hundreds of components [226], many of which have properties that have the potential to help treat various types of disease or have various modes of action against a specific disease and its consequences [233–235]. Another consideration is that a strong specific effect, such as that of an anticoagulant used in an effort to prevent the microthromboses that have become a serious consequence of advanced COVID19 [236], requires specific dosing in order to avoid excess bleeding and other dangerous side effects [237], and such drugs are not a safe option for patients that have some types of blood disease, or various heart and vessel disorders. A natural anticoagulant could give some protection and at a level sufficient to reduce the risk of thrombosis without strong side effects. Propolis has demonstrated anticoagulant properties [147].

15. Conclusions

Considering the large number of deaths and other types of damage that the COVID-19 pandemic is causing, there is an urgent need to find therapies that can help avoid or reduce SARS-CoV-2 infection and its consequences. Propolis has proven anti-inflammatory and immunoregulatory effects, including PAK-1 inhibition. Also, attachment to ACE2, a major target of the SARS-CoV-2 virus for host cell invasion, is inhibited by propolis. Propolis components, including CAPE, rutin, quercetin, kaempferol and myricetin have demonstrated *in silico* a strong interaction with ACE2. Kaempferol reduced the expression of TMPRSS2. In addition to these activities, propolis does not interact with the main liver enzymes or with other key enzymes; according to criteria adopted by the World Health Organization, therefore propolis can be used concurrently with the main drugs without risk of potentiation or inactivation.

To determine if propolis specifically affects SARS-CoV-2 will require more research. But given that propolis is a risk-free product, except for those who may develop an allergy to it, the known biological activities of this natural bee product lead us to suggest its use for reducing the risk and impact of infection and as an adjunct to treatment.

Declaration of Competing Interest

The authors declare no conflict of interest.

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