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REVIEW ARTICLE

Propolis efficacy on SARS-COV viruses: a review on antimicrobial activities and molecular simulations

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Abstract

This current study review provides a brief review of a natural bee product known as propolis and its relevance toward combating SARS-CoV viruses. Propolis has been utilized in medicinal products for centuries due to its excellent biological properties. These include anti-oxidant, immunomodulatory, anti-inflammatory, anti-viral, anti-fungal, and bactericidal activities. Furthermore, studies on molecular simulations show that flavonoids in propolis may reduce viral replication. While further research is needed to validate this theory, it has been observed that COVID-19 patients receiving propolis show earlier viral clearance, enhanced symptom recovery, quicker discharge from hospitals, and a reduced mortality rate relative to other patients. As a result, it appears that propolis could probably be useful in the treatment of SARS-CoV-2-infected patients. Therefore, this review sought to explore the natural properties of propolis and further evaluated past studies that investigated propolis as an alternative product for the treatment of COVID-19 symptoms. In addition, the review also highlights the possible mode of propolis action as well as molecular simulations of propolis compounds that may interact with the SARS-CoV-2 virus. The activity of propolis compounds in decreasing the impact of COVID-19-related comorbidities, the possible roles of such compounds as COVID-19 vaccine adjuvants, and the use of nutraceuticals in COVID-19 treatment, instead of pharmaceuticals, has also been discussed.

Keywords COVID-19 · SARS-CoV-2 · Vaccine · Propolis · Molecular simulation · Pharmacological properties · Antimicrobial activities

Introduction

The novel 2019 coronavirus (formally referred to as "SARS-CoV-2") is one of several viruses that are notorious for causing various respiratory illnesses, particularly in human populations. The other viruses include influenza A, Middle East respiratory syndrome coronavirus (MERS-COV), and severe acute respiratory syndrome coronavirus (SARS-COV). Just like the other three indicated viruses (Abdelrahman et al. 2020; Mohammadbeigi et al. 2020), SARS-CoV-2 has also caused a global pandemic that started around December 2019 (Alhouri et al. 2020; Lu et al. 2020; Zhu et al. 2020; Ghosh et al. 2021; Meskini et al. 2021). By the first week of July 2021, the SARS-CoV-2, which causes a disease called COVID-19, was still ongoing with more than 185 million positive cases and over four million deaths having been recorded globally (Johns Hopkins University & Medicine Coronavirus Resource Center; https://coronavirus.jhu.edu/map.html). During that period, pharmaceutical companies had tested several vaccines and some have since been authorized for vaccinating citizens in different countries throughout the world. While SARS-CoV-2 vaccines are generally safe and effective (Polack et al. 2020; Anand and Stahel 2021), public acceptance among the general population and healthcare workers has been worryingly low in some countries (Kreps and Kriner 2021; Sallam 2021). Cited reasons for general vaccine hesitancy included cognitive, psychologic, socio-demographic, and cultural factors. In addition, the lack of sufficient infrastructure to receive and administer vaccines creates an impediment to vaccination programmes

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in rural and remote areas of countries, particularly in Africa (Nachega et al. 2021). Alternative treatment methods may help bridge the divide between modern treatments, traditional herbal medicines, and cultural beliefs.

One of the oldest known folk medicines is propolis, a wax-like resinous substance used by various nations since ancient times (Kuropatnicki et al. 2013; Toreti et al. 2013). Bees, especially the Western or European honeybee (*Apis mellifera*) and related subspecies, collect resins and pollen from various plants and combine these compounds with wax to produce propolis (Ahangari et al. 2018). Propolis serves many functions in bee colonies, including usage in sealing cracks or crevices as well as repairing combs in hives, protecting hives against weather elements, moisture control in hives, and providing antimicrobial protection for the larvae. In human and animal societies, propolis has been shown to exude many medicinal and therapeutic properties (Kuropatnicki et al. 2013; Toreti et al. 2013; Wagh, 2013; Mahmoud et al. 2016; Pasupuleti et al. 2017; Ahangari et al. 2018; Anjum et al. 2019; Zulhendri et al. 2021). Interestingly, such properties tend to vary depending on the chemical composition of propolis in line with plant and bee species occurring in the geographical source area (Toreti et al. 2013; Wagh 2013; Zulhendri et al. 2021). That around 3,000 propolis-related patents have been filed thus far (Toreti et al. 2013; de Carvalho Furtado et al. 2018) demonstrates the enormous potential that this compound holds in benefiting human populations, especially the treatment of novel diseases.

The current review specifically sought to address the roles that propolis can play as an anti-bacterial, anti-fungal, and anti-viral in human societies. Particularly, much emphasis was placed on the anti-viral properties of propolis, the possible mode of compound actions based on molecular simulations of propolis compounds that interact with the SARS-CoV-2 virus. Limitations on the use of propolis for medicinal purposes and its potential as a nutraceutical have also been discussed.

SARS-COV virus family and COVID-19

The ancestor of all coronaviruses is believed to have occurred approximately 8,000 BCE, even though several models inferred long-term evolution that was traced to the common ancestor ~ 55 million years ago (ref.). Coronaviridae is a positive sense, single-strand RNA genome family that infects animals including birds, amphibians, and mammals (Holmes 1999). The coronaviridae was identified as a new virus family in 1968, because of the intracellular budding and distinct site virion morphology (ref.). Characteristic features of their replication strategy, genome, DNA polymerase, and structural proteins were also considered for classifying members of the coronaviridae (Fig. 1).

The coronaviridae, arterviridae, mesoniviridae, and roniviridae are recognized as separate families within the sub-order cornidovirineae (Srivastava and Saxena 2020). Orthocoronavirinae and torovirinae are recognized as separate sub-families within the coronaviridae family (Decaro and Lorusso 2020; Li et al. 2020a), whereas the alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus are classified as members of the orthocoronavirinae sub-family (Zaim et al. 2020).

Currently, the coronaviridae family comprises two sub-families, six genera, 26 sub-genera, and 46 species. Further species descriptions are tentative or pending (Siddell et al. 2019; Igori et al. 2020). Human coronaviruses (CoV) are a huge family that are capable of causing diseases ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) (Liu et al. 2020). A novel coronavirus (nCoV) is a new strain within the coronaviridae family that had not been identified before, and it causes the coronavirus disease. The disease (named COVID-19) initially emerged in China around December 2019. Soon after, it was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020 (Cascella et al. 2022).

COVID-19 is caused by the seventh known coronavirus that is capable of infecting humans, with the predecessors including 229E, NL63, OC43, HKU1, MERS-CoV, and the original SARS-CoV (Boni et al. 2020). Coronaviruses cause zoonotic diseases that can be transmitted between human and animals. Seemingly, MERS-CoV was transmitted from dromedary camels to humans, whereas SARS-CoV moved from civet cats to humans, and SARS-CoV-2 from bat to humans. Several known coronaviruses circulate in various animals that have not infected humans yet (Ye et al. 2020). Notably, the reports indicated the fatality rate of MERS is about 34%; however, the SARS-CoV is ~ 11–14% indicating that the death rate of MERS is much higher than the SARS-CoV (Mohammadi et al. 2022; Meskini et al. 2021).

Natural products in medical science

Historically, natural products are widely used to avoid and alleviate diseases (Bakkali et al. 2008; Saklani and Kutty 2008; Nahar and Sarker 2020). This is due to the fact that natural products tend to be reasonably priced, commonly available and rarely show undesirable side effects (Berretta et al. 2020). While natural products command significant interest in the fields of biomedical research and technology, researchers and physicians appear to be somewhat reluctant to explore their properties further, perhaps due to lack of knowledge on biomimicry (Scorza and Cavalheiro

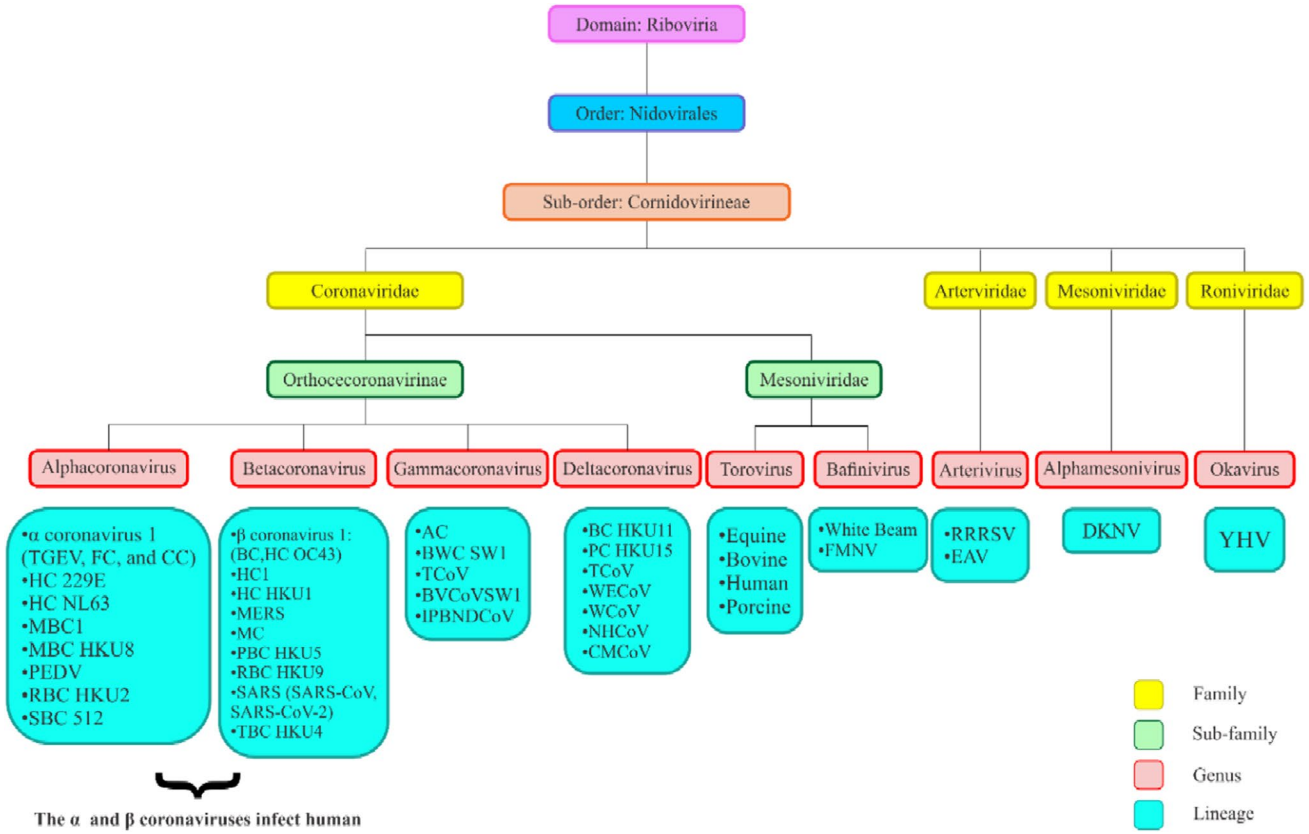
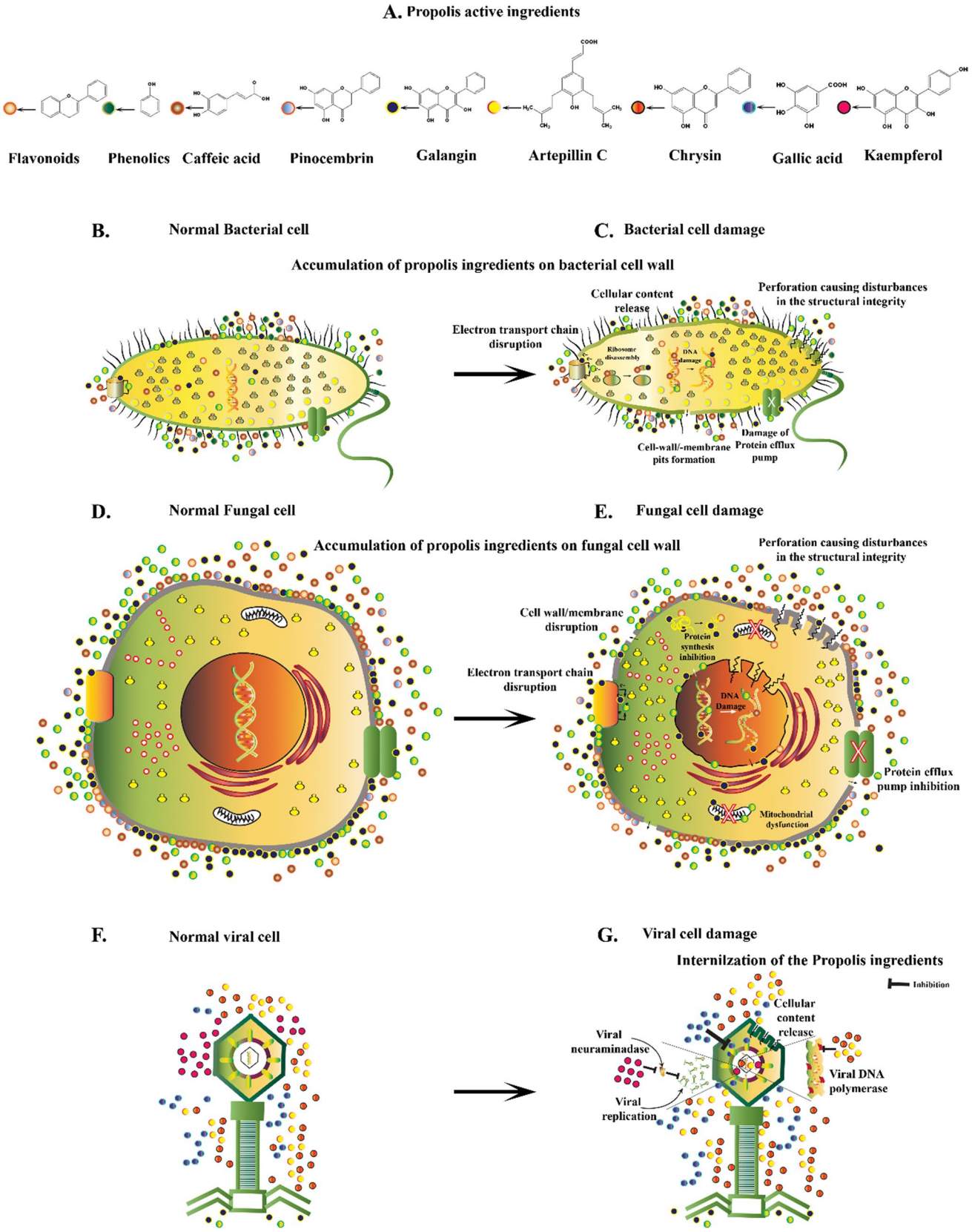


Fig. 1 Coronaviridae family classification. Genus: Alphacoronavirus: α coronavirus 1 (TGEV, FC: feline coronavirus, CC: canine coronavirus), HC 229E: human coronavirus 229E, HC NL63: human coronavirus NL63, MBC1: Miniopterus bat coronavirus 1, MBC HKU8: Miniopterus bat coronavirus HKU8, PEDV: Porcine epidemic diarrhea virus, RBC HKU2: Rhinolophus bat coronavirus HKU2, and SBC 512: Scotophilus bat coronavirus 512 (Decaro 2011). Genus Betacoronavirus; βcoronavirus 1 (BC:Bovine Coronavirus,HC OC43: Human coronavirus OC43), HC1: Hedgehog coronavirus 1, HC HKU1: Human coronavirus HKU1, MERS: Middle East respiratory syndrome-related coronavirus, MC: Murine coronavirus, PBC HKU5: Pipistrellus bat coronavirus HKU5, RBC HKU9: Rousettus bat coronavirus HKU9, SARS: Severe acute respiratory syndrome–related coronavirus (SARS-CoV, SARS-CoV-2), and TBC HKU4: Tylonycteris bat coronavirus HKU4 (Decaro 2011). Genus Gammacoronavirus;[18]: AC: Avian coronavirus, BWC SW1: Beluga whale coronavirus SW1, TCoV: Turkey coronavirus, BVCoVSW1: Beluga whale CoV SW1, and IPBNDCoV: Indo Pacific Botthe Nose Dolphins CoV (Decaro 2011). Genus Deltacoronavirus: BC HKU11: Bulbul coronavirus HKU11, PC HKU15: Porcine coronavirus HKU15, TCoV: Thrush CoV, WECoV: White Eye CoV, WCoV: Wigeeon CoV, NHCoV: Night Heron CoV, and CMCoV: Commen Moorhen CoV (Fan et al. 2019). FMNV: Fathead Minnow Nido Virus (Baird and Faisal 2016). PRRV: Porcine reproductive and respiratory syndrome (Lyoo 2015), EAV: Equine arteritis virus (Snijder et al. 1995). DKNV: Dak Nong virus (Warrilow et al. 2014). YHV: yellow head virus (Enjuanes et al. 2008)

2010; Scorza et al. 2020; Benyus 2021). Some researchers, however, observed extensive evidence supporting the use of propolis, a well-known bee product that serves as a bioactive food component used in dietary supplements for nutrition and health-related purposes (Shaha et al. 2018; Ali and Kunugi 2019, 2020b; Egawa et al. 2019; Boisard et al. 2020). Seemingly, propolis could potentially be used in the treatment for SARS-CoV-2 patients because it exudes specific and relevant characteristics including anti-inflammatory action, ability to reduce viral replication and immune system fortification (Ansorge et al. 2003; Shimizu et al. 2011; Machado et al. 2012; Chan et al. 2013; Hori et al. 2013).

Properties of propolis

Propolis is defined as a natural product that is sourced from plant resins and other plant exudates such as flower buds (Ali and Kunugi 2020a;b). Typically, plants protect themselves from pathogens by producing phytochemicals. Chemical substances such as terpenoids and phenols are present as phytochemicals, are collected by bees (Langenheim 1994; Cheng et al. 2007; Toreti et al. 2013). Propolis contains more than 300 phytochemical compounds (Kocot et al. 2018; Anjum et al. 2019; Ali and Kunugi, 2020a; Hashem 2020), and these include caffeic acid, myricetin, and quercetin—all of which are known to inhibit coronavirus activity in humans (Wang et al. 2018; Ali and Kunugi 2020b; Mani


A. Propolis active ingredients
Flavonoids
Phenolics
Caffeic acid
Pinocembrin
Galangin
Artepillin C
Chrysin
Gallic acid
Kaempferol
B. Normal Bacterial cell
C. Bacterial cell damage
Accumulation of propolis ingredients on bacterial cell wall
Cellular content release
Perforation causing disturbances in the structural integrity
Electron transport chain disruption
Ribosome disassembly
DNA damage
Cell-wall/-membrane pits formation
Damage of Protein efflux pump
D. Normal Fungal cell
E. Fungal cell damage
Accumulation of propolis ingredients on fungal cell wall
Perforation causing disturbances in the structural integrity
Cell wall/membrane disruption
Protein synthesis inhibition
Electron transport chain disruption
DNA Damage
Protein efflux pump inhibition
Mitochondrial dysfunction
F. Normal viral cell
G. Viral cell damage
Internilzation of the Propolis ingredients
Inhibition
Cellular content release
Viral neuraminadase
Viral DNA polymerase
Viral replication

◂**Fig. 2** Antimicrobial activities of the propolis active ingredients. **A.** Chemical structure of the active ingredients of propolis indicated by the colored circles. **B.** Normal bacterial cell. **C.** Antibacterial activities of the propolis ingredients causing leakage and shrinkage of the cell with disruptions in multiple organelles. **D.** Normal fungal cell. **E.** Accumulation and perforation of the propolis ingredients into the fungal cell causing cellular perturbation with disruption of their organelles. **F.** Normal viral cell. **G.** The propolis ingredients causing antiviral effect by inhibiting the viral spike proteins, neuraminidase and DNA polymerase prohibiting them to infect the host cell, viral replication and DNA replication respectively

et al. 2020; Guler et al. 2021). However, it must be noted that the composition active components in propolis may vary at different geographical locations (Bankova 2005; Falcao et al. 2013; Toreti et al. 2013; Miguel et al. 2014; Ali and Kunugi 2020b; Hashem 2020). Nevertheless, honeybees can identify the anti-microbial characteristics of certain plants, and therefore, selectively collect and process flower material from chosen plants to produce propolis (Simone-Finstrom and Spivak 2010).

Overall, propolis possesses anti-cancer, anti-oxidant, immunomodulatory, anti-inflammatory, anti-bacterial, anti-fungal as well as antiviral properties (Berretta et al. 2012). As a result, it has been used widely for alleviating various diseases (Cowan 1999; Ramos and Miranda 2007; Bakkali et al. 2008; Saklani and Kutty 2008). Maruta and He proposed that propolis should be considered as an adjunct treatment for SARS-CoV-2 (Maruta and He 2020). This is mostly due to propolis being economical, commonly accessible, and hardly presenting unwanted side effects (Berretta et al. 2017).

Anti-microbial activities of propolis

Many studies have demonstrated the anti-microbial effects of propolis (Al-Ani et al. 2018a; Karadal et al. 2018). Certainly, propolis possesses anti-microbial properties including anti-bacterial, anti-fungal and anti-viral effects due to the presence of bioactive compounds (e.g., phenolics and flavonoids) present in its extracts (Uzel et al. 2005; Suleman et al. 2015; Al-Ani et al. 2018a; Karadal et al. 2018) (Fig. 2A). Moreover, there seems to be a correlation among the efficacy of propolis and the botanical source and geographical origin of its components (Al-Ani et al. 2018a). Propolis isolated from temperate zones seemingly possess stronger anti-microbial activity due to the higher content of phenolic compounds (46.45 ± 3.1 mg CAE/g—129.83 ± 5.9 mg CAE/g) and flavonoids (0.11 ± 0.01 mg QE/g -2.86 ± 0.2 mg QE/g) (Ramanauskien et al. 2009; Rahman and Richardson 2010; Al-Ani et al. 2018b; Karadal et al. 2018). It is, thus, not surprising that propolis samples with low phenolic contents are generally less effective towards Gram-negative bacteria (Almuhayawi 2020).

Other factors that influence the efficacy of propolis against microbes include the type of microorganisms (strain) tested and concentration of propolis examined (Petruzzi et al. 2020). Notably, microbes have different resistance mechanisms to anti-microbial compounds (Reygaert 2018), and similarly, some microbes show stronger resistance to propolis than others (Almuhayawi 2020). In general, the concentration of an anti-microbial agent plays a pivotal role in resistance mechanisms of microbes (Li et al. 2017). For example, low concentrations (20,000–300,000 ppm) of propolis can be effective against Gram-positive bacteria (Petruzzi et al. 2020). Conversely, the growth of Gram-negative bacteria is mostly inhibited at higher concentrations of propolis. These findings suggest that the bacterium being investigated will require high amounts than the indicated studies of active compounds in propolis to initiate effective anti-microbial action.

Anti-bacterial

Both Gram-positive and Gram-negative bacteria have been investigated for their susceptibility towards propolis (Bankova et al. 2014). However, there is a consensus that Gram-negative bacteria are more resistant towards propolis than Gram positive bacteria (Campos et al. 2015; Przybyłek and Karpiński 2019; Petruzzi et al. 2020). For instance, propolis could inhibit *Staphylococcus aureus* (Gram-positive bacteria), but it exhibited limited action against Gram-negative *Escherichia coli* (Muli and Maingi 2007; Pobiega et al. 2019). In fact, the microbial inhibitory concentration (MIC) values in tests involving propolis are generally higher for Gram-negative bacteria (Al-Ani et al. 2018a). The resistance mechanism of Gram-negative bacteria could probably be attributed towards structural and biochemical differences in the cell wall composition (Ghasemi et al. 2017).

In general, Gram-negative bacteria are more resistant to antibiotics such as carbapenems, quinoles, cephalosporins, polymxins, and other β-lactam antibiotics that are commonly used to treat bacterial infections (Miller 2016; Breijyeh et al. 2020) or anti-microbial effects (Lee et al. 2007). The resistant mechanism of Gram-negative bacteria to propolis may be due to the efflux pumps on the bacterial cell wall that prevent the intracellular accumulation of propolis constituents (Petruzzi et al. 2020). Similarly, the production of hydrolytic enzymes that break down active compounds in propolis may contribute to the resistance mechanisms displayed by Gram-negative bacteria (Przybyłek and Karpiński 2019). Nonetheless, recent evidence shows that propolis may also be effective against Gram-negative bacteria, developments that further illustrate the versatility of propolis as an anti-microbial agent (Ramanauskien et al. 2009; Suleman et al.

2015; Karadal et al. 2018; Abdullah et al. 2019). However, there seems to be inconsistencies in the literature regarding the overall efficacy of propolis against Gram-negative bacteria. For example, several authors have reported that propolis is ineffective against the popular Gram-negative bacterium, *E. coli* (Ramanauskien et al. 2009; Gajger et al. 2017). Equally, other studies have demonstrated minimal to moderate susceptibility (Suleman et al. 2015; Karadal et al. 2018; Abdullah et al. 2019). However, other Gram-negative bacteria seem to show moderate to complete inhibition (Ramanauskien et al. 2009). At the other end, for Gram-positive bacteria, propolis is much more effective with species such as *Staphylococcus aureus*, *Bacillus subtilis*, *Bifidobacteria spp.*, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus sobrinus*, and *Listeria monocytogenes*, demonstrating high susceptibility (Fernandes Jr et al. 2005; Uzel et al. 2005; Rahman and Richardson 2010; Morawiec et al. 2015; Al-Ani et al. 2018a; Grecka et al. 2019). The species *L. monocytogenes* was initially reported to be resistant to propolis extracts, a finding that has since changed as the bacterium is susceptible (Temiz et al. 2011; Ristivojević et al. 2016; Karadal et al. 2018).

The anti-bacterial mechanism of propolis has been attributed to its constituent compounds including flavonoids(e.g., pinocembrin and galangin) and phenolics, (e.g., caffeic acid) (Rahman and Richardson 2010; Anjum et al. 2019; Gür et al. 2020). Typically, phenolic compounds can bind to various bacterial proteins and peptides effectively, resulting in the alteration of their 3D structures and functional inhibition (Bouarab-Chibane et al. 2019). The mechanism employed by propolis toward bacteria includes the inhibition of cell division, cell membrane collapse, enzymatic inactivation, the inhibition of protein synthesis (translation), and cell death through bacteriolysis (Fig. 2B, C). Using two Italian propolis samples, Bosio and co-workers reported that the key compounds that presented anti-bacterial activity against *Staphylococcus pyogenes* were galangin and pinocembrin (Bosio et al. 2000). Moreover, propolis exhibited anti-microbial activity against *S. aureus* through translation inhibition processes (Grecka et al. 2019). Conclusively, it has been observed that the antibacterial activities of propolis is comparable or better than commercially available antibiotics (Muli and Maingi 2007).

Anti-fungal

Anti-fungal effects of propolis have been reported in genera including *Aspergillus*, *Furisia*, *Candida*, *Alternaría*, *Trichosporon*, *Rhodotorula*, *Saccharomyces*, *Cryptococcus*, and *Pseudoascus* (Özcan 1999; Silici et al. 2005; Oliveira et al. 2006; Koc et al. 2007; Suleman et al. 2015; Ghosh et al. 2018; Bezerra et al. 2020). In one study, propolis moderately inhibited *Furisia oxysporum* spores probably due to the presence of phenolic acids and flavonoids (Petruzzi et al. 2020). These compounds act on *F. oxysporum* by making the cytoplasmic membrane permeable (Ahmed et al. 2008). Usually, this process will lead to the leakage of vital cellular components including proteins, nucleic acids and inorganic ions, which would induce cell death (Wang et al. 2021). Notably, propolis extracts in the study were highly effective to the fungal species than the bacterial counterparts (Petruzzi et al. 2020). Kambiz et al. (2013) reported that propolis extracts at a concentration of 0.125 g/L demonstrated effective anti-fungal activity against *Aspergillus niger*, which resulted in morphological changes on the cell membrane (Fig. 2D, E). In general, ethanol-based extracts of propolis tend to target cell membranes of fungi (Petruzzi et al. 2020).

Anti-fungal studies of propolis were generally focused on yeast-like fungi in the genus *Candida*, with most showing the anti-candidiasis effects of propolis (Yusoff et al. 2016; de Castro et al. 2013; Gucwa et al. 2018). Specifically, propolis extracts may inhibit the *Candida* switchover from yeast-like to hyphal growth, which effectively suppresses biofilm formation (de Castro et al. 2013; Tobaldini-Valerio et al. 2016). In such instances, the biofilm would aggregate as non-contiguous cells rather than pseudohyphae (Capoci et al. 2015). Elsewhere, propolis extracts exhibited higher anti-candidial activity compared to known anti-candida drugs such as azoles and amphotericin B (Gucwa et al. 2018). Another study hypothesized that chlorogenic acid, a derivative of caffeic acid, may disrupt the fungal cell membranes, leading to leakage of vital cytoplasmic contents (Sung and Lee 2010). Thus, there seems to be an inverse correlation between active compounds in propolis and anti-fungal activity (Fig. 2D, E). Phenolic compounds, on the other hand, could inhibit fungal growth by suppressing mitochondrial activity in the fungus (Gallucci et al. 2014).

Anti-viral

Besides anti-microbial activity against bacteria and fungi, propolis extracts have further demonstrated activity against viruses. For instance, such anti-viral effects were observed against viruses including herpes simplex virus (HSV), human rhinovirus, influenza A and B viruses, adenovirus, polio virus, rotavirus, human immune deficiency virus (HIV), human papillomavirus, vesicular stomatitis virus, Newcastle disease virus, and coronavirus (Debiaggi et al. 1990; Iljazović et al. 2006; Shimizu et al. 2008, 2011; Búfalo et al. 2009; da Silva et al. 2019; Kwon et al. 2020; Fiorini et al. 2021). In fact, current scientific evidence supports the effectiveness of propolis to inhibit and/or kill viruses (Fiorini et al. 2021).

Various compounds in propolis extracts show anti-viral properties against different viruses. Yildirim et al. (2016) showed that artepillin C and chrysin affect the replication

of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) by targeting the viral DNA polymerase (Shnitzler et al. 2008; Coelho et al. 2015; Fiorini et al. 2021) (Fig. 2F,G). Actually, propolis extracts have higher anti-viral activities against HSV-1 and HSV-2, as compared to acyclovir (Shimizu et al. 2011). The anti-viral activity of propolis against human rhinoviruses was putatively caused by gallic acid (Sithisarn et al. 2013; Khalil and Tazeddinova 2020; Kwon et al. 2020), whose mode of action relates to the inhibition of virus adsorption (Choi et al. 2010). Kai and co-workers similarly demonstrated the anti-viral activity of propolis against influenza virus strains, both in vitro and in vivo (Kai et al. 2014). The authors found that kaempferol inhibits viral growth by suppressing viral replication (Kai et al. 2014; Zhang et al. 2017a). Typically, kaempferol acts on the viral neuraminidase protein as described by Jeong et al. (2009) and Sithisarn et al. 2013 (Fig. 2F,G). Regarding HIV, Harish et al. (1997) reported that propolis could suppress HIV-1 replication processes probably due to the kaempferol. In the same way, propolis extracts at concentrations up to 66.6 µg/mL inhibited HIV activity in $CD4^+$ cells and microglial cell cultures (Gekker et al. 2005). In addition, the compound acts by inhibiting the viral reverse transcriptase activity (Behbahani et al. 2014; Zakaryan et al. 2017) (Fig. 2F,G). Altogether, these anti-viral activity have the potential for effective and novel properties against a variety of viruses including coronavirus. Indeed, propolis acts against cutaneous warts with an efficacy of up to 75% (Zedan et al. 2009). In this instance, propolis acted as an immunomodulator to lessen warts.

The necessity of propolis in mitigating COVID-19

With over 231,091,474 confirmed cases (Worldometer 2021), the worldwide pandemic of COVID-19 has become a highly infectious disease that attributed to the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pathogen (Goyal and Goyal 2020; Maaroufi 2020). Currently, 4,736,031 people have lost their lives due to the virus (Worldometer 2021) and the pandemic is recognized as having a significant impact on economic sectors involving human health, global finances as well as the environment (Cheval et al. 2020; Cullen et al. 2020; Gautam and Hens 2020; Hassan et al. 2020). It is believed that this virus is more deadly than other types of viruses causing common diseases (Vardeny et al. 2020). Around the world, several unusual measures have taken place, including the long-term closure of commercial businesses, educational institutions, and tourism sites (Yang and Wong 2020; Pokhrel and Chhetri 2021; Barua 2020). In an attempt to recover from disruptions caused by COVID-19 and mitigate against the impact of the pandemic, several biomedical health strategies have been implemented. These include the production and provision of vaccines (Koff et al. 2021; Onyeaka et al. 2021) as well as the implementation of numerous protective measures aimed at preventing the continuous spread of the disease (Pradhan et al. 2020). Although the production of vaccines is increasing, the demand for these vaccines is massive and many challenges remain (Koff et al. 2021; Onyeaka et al. 2021). Simultaneously, some preventive measures have limited efficacy (e.g., insert), which further lead to an increase in viral spreading (Corburn et al. 2020; Pereira et al. 2020; Setti et al. 2020; Lapolla et al. 2021). A number of alternative medicinal treatment regimens have been proposed and investigated, but most of these options need further validation and approval before being distributed and utilized (Sanders et al. 2020).

While a precise treatment plan for COVID-19 patients is presently lacking, consistent amendment of existing strategies is the utmost requirement in clinical treatment scenarios. Remedies including the use of blood transfusion-related technologies, convalescent plasma transfusion, anti-malarial agents, antibiotics, anti-viral therapy, and immunomodulatory agents have been approved and implemented in current medical practices (Li et al. 2020b). Translational research has concurrently been performed to develop a safe vaccine that can be used for combating SARS-CoV-2 infections globally (Moore and Klasse 2020). Furthermore, therapies involving plants and novel organic molecules sourced from different plants have crucially demonstrated repressive anti-viral activity against SARS-CoV-2 (Serkedjieva et al. 1992; Calixto 2000; 2005; Maruta and He 2020; Orhan and Senol Deniz 2020).

Case studies on the usage of propolis against SARS-CoV-2 virus

Fiorini et al. 2021 (Fiorini et al. 2021) investigated the case of a 52 year-old woman who had tested positive for COVID-19. The patient suffered from common symptoms of COVID-19 including malaise, sore throat, and headache. She did not have any history of persistent illnesses. Blood tests yielded results that were within a usual reference range. As is generally recommended, the woman was advised to quarantine at home for 14 days. During that period, she consumed Brazilian green propolis at a dosage of 45 drops, thrice per day for the entire 14 days, along with healthy food and sufficient hydration. Eventually, the patient recovered from the viral infection by testing negative through the reverse transcription-polymerase chain reaction (RT-PCR) assay for SARS-CoV-2. Although the relevance of propolis and its therapeutic intervention is debatable as these results are based on a single case, it can still be argued

that propolis may have offered some therapeutic benefits to the patient. Ali et al. (Ali and Kunugi 2021) theorized that among COVID-19 patients, propolis, and mixtures of honey associated with enhanced viral clearance and recovery from symptoms. In addition, the patients were overall discharged from healthcare facilities earlier than other patients and presented low mortality rates. However, since a combination of bee products were used, the performance of propolis in the treatment remains unclear. As such, the effect of individual bee products must be further investigated.

Possible mode of propolis action against SARS-COV viruses

Propolis contains various compounds that are responsible for different pharmacological properties. Among these, notable compounds are the hydroxycinnamic acids (p-coumaric acid, ferulic acid), phenols, and terpenoids. Additionally, there are also flavonoids such as quercetin, t-farnesol, caffeic acid fenethyl ester (CAPE), apigenin, luteolin, artepillin C, resveratrol, withanone, naringenin as well as caretonoids such as lutein (Chirumbolo 2011; Salonen et al. 2012; Kumazawa 2018).

Various components in propolis have been shown to interact with the SARS-CoV-2 virus. For example, Kumar et al. (Kumar et al. 2020) presented models showing the interaction between CAPEs and the SARS-CoV-2 protease to cause an inhibitory effect on the virus. Similarly, in vitro assays involving quercetin showed that it inhibited proteases in SARS-CoV-1 and MERS-CoV (Bachevski et al. 2020). CAPE further inhibits NF-kB (nuclear factor of kappa chains of B cells) molecules, which are responsible for controlling the transcription and regulation of immune response mechanism to viral antigens. This eventually increases the production of lymphocytes and antibodies, in accordance with in vitro studies. CAPE has also been shown to possess anti-inflammatory activity, reduces cytokine production and inhibits PAK1 (activated protein kinase) by blocking the ACE1 (angiotensin converting enzyme1) and the virus's main protease enzyme called M^{pro}. In addition, CAPE inhibits type II transmembrane serine proteases (TMPRSS2), whose main function is to facilitate viral entry into the cell. Elsewhere, CAPE seems to inhibit pulmonary fibrosis that is produced by coronaviruses (Maruta and He 2020). Quercetin, on the other hand, could have an inhibitory effect on SARS-CoV-2 by inhibiting the viral polymerase and further prevent replication when in combination with vitamin C. Additionally, quercetin and zinc are capable of blocking viral reproduction (Bachevski et al. 2020; Biancatelli et al. 2020) (Fig. 3).

Phenolic compounds in propolis seemingly stimulate the production of interferons, which act on different viruses including avian influenza, HSV, Newcastle, and HIV-1 (Amoros et al. 1992; Harish et al. 1997; Shimizu et al. 2008; Fan et al. 2011). In addition to antiviral activities, kaempferol also has anti-inflammatory properties, which emerge through the decrease of tumor necrosis factor-alpha and cytokine production. It may also reduce the expression of TMPRSS2 and inhibit viral attachment to the main ACE2 receptor on human T cells. Crucially, kaempferol also acts on the main protease M^{pro} of the SARS-COV viruses (Schwarz et al. 2014; Solnier and Fladerer 2020) (Fig. 3).

Hesperetin is one of the most active polyphenols in propolis that also occurs in citrus juice (Lu et al. 2004; Muhammad et al. 2019). Notably, it has affinity for the ACE2 receptor, whereby after attachment, it will interfere with viral entry into the host cell and also interact with the viral enzymes M^{pro} and/or 3 CL pro (Bellavite and Donzelli 2020; Haggag et al. 2020). On the other hand, the flavonoid naringenin exhibits antiviral effects by interfering with viral entry into the cell, and thereby preventing its replication and addition to inhibiting proteases as well as acting on ion channels (Alberca et al. 2020; Clementi et al. 2021). Resveratrol and pterostilbene have antiviral properties against HIV-1, influenza, dengue virus, Zika virus as well as MERS-CoV and SARS-CoV-2 (Chan et al. 2017). In vitro studies involving the two compounds indicate effective antiviral properties by directly intervening in viral replication and decreasing expression of the ACE2 and DDP4 receptor proteins, which are required for viral entry into the host cell (Chan et al. 2017; Mattio et al. 2020; ter Ellen et al. 2021). In summary, the antiviral mechanisms of these compounds are responsible for the inhibition of viral proteases, some of which are considered as part of therapeutic strategies in clinical trials with lopinavir-ritonavir (Hung et al. 2020) (Fig. 3).

Molecular simulations of propolis compounds interacting with SARS-CoV-2

Compounds extracted from natural products are of great interest in the treatment of various diseases. To this end, several authors investigated the efficiency of natural products as potential treatments against the SARS-CoV-2 viral infection using different approaches (Merarchi et al. 2021; Romeo et al. 2021). Among the natural products used as anti-SARS-CoV-2, compounds extracted from propolis have been reported to be very promising (Berretta et al. 2020). Experimental testing of all propolis compounds against SARS-CoV-2 will surely be time and resource consuming. Therefore, computational studies have been performed to quickly identify and assess the performance of some compounds in binding and inhibiting active sites of the SARS-CoV-2 virus. Most computational assessments were performed using molecular docking to calculate the binding

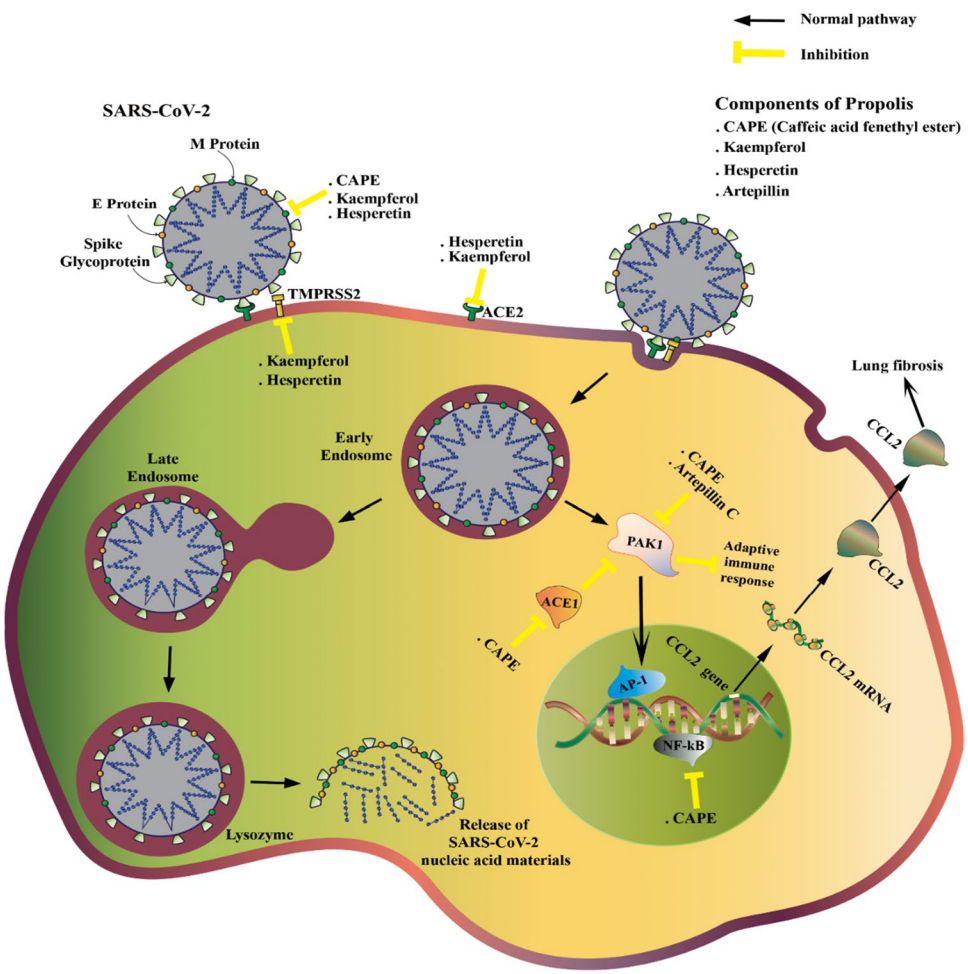


Fig. 3 Molecular mechanisms of propolis for the anti-SARS-COV-2 activities. Depicts the major pathways that propolis derived components interacts and inhibits the SARS-CoV-2 to the host cell, their replication and pathophysiological consequences. SARS-CoV-2 spike protein binds to the ACE2 receptor of the target host cell and gets activated by TMPRSS2. Following the binding, the viral endocytosis occurs followed by the activation of the PAK1 that reduces the adaptive immune response and antibody production against the virus. PAK1 also stimulates CCL2 production causing lungs fibrosis. Concurrently, the viral infection also induces NF-kB activation, causing pro-inflammatory cytokines overproduction. Propolis active ingredients downregulate and ACE2 and TMPRSS2 that restrict the virus entry to the cell. Furthermore, they reduce the PAK1 activation, increasing the antibodies against SARS-CoV-2. Also, the CAPE inhibits the NF-kB causing monocyte/macrophage immodulation, reducing pro-inflammatory cytokine overproduction

energies of various compounds at the active sites of SARS-CoV-2 (Berretta et al. 2020).

Ellagic acid extracted from honey and propolis has been found to form strong hydrogen bonds with Tyr831, Gly808, Thr817, His816, and Pro809 residues of the RNA-dependent RNA-polymerase in SARS-CoV-2 (Shaldam et al. 2021) (Fig. 4). Using molecular docking, it has been found that ellagic acid, p-coumaric acid, quercetin, and kaempferol strongly bind to the SARS-CoV-2 RNA-dependent RNA-polymerase. Specifically, ellagic acid has a highest binding score against the SARS-CoV-2 RNA-dependent RNA-polymerase, whereas kaempferol has showed the highest binding score against the main protease in SARS-CoV-2. In another study, Sahlan and co-workers performed molecular docking simulations to identify compounds in Sulawesi propolis that can inhibit the main protease in SARS-CoV-2 (Sahlan et al. 2019). They found that glyasperin A and broussoflavonol F can bind to the main protease strongly. Thus, the two compounds were identified as potential candidates for treatment against COVID-19 (Sahlan et al. 2019). Furthermore, extracts from Sulawesi propolis were further reported to be potential inhibitors of ACE2 through the molecular docking approach. Glyasperin A, sulabiroins A, broussoflavonol F, and isorhamnetin specifically showed the potential to inhibit ACE2 and SARS-CoV-2, with binding scores higher than 9.2 kcal/mol (Khayrani et al. 2021). Kumar et al. (Kumar et al. 2020) investigated the performance of aferine A and anone as anti-SARS-CoV-2 compounds. They found that both compounds can bind and inhibit the transmembrane protease serine 2 (TMPRSS2) (Kumar et al. 2020). Chrysin, another compound extracted from honey bee propolis, was also reported to interact with ACE2 and the SARS-CoV-2 spike protein through the molecular docking approach (Basu et al. 2020).

Although molecular docking simulations and screenings are necessary for the initial assessment of compounds' binding energies, further investigations are still needed to confirm the efficiency of identified compounds at the molecular level. Evidence gathered from the literature suggests that molecular dynamic simulations with proper choice of force fields have not been applied when assessing potential anti-SARS-CoV-2 compounds extracted from propolis. Thus, studies on molecular dynamic simulations with careful choice of fitted force fields will be awaited keenly. To

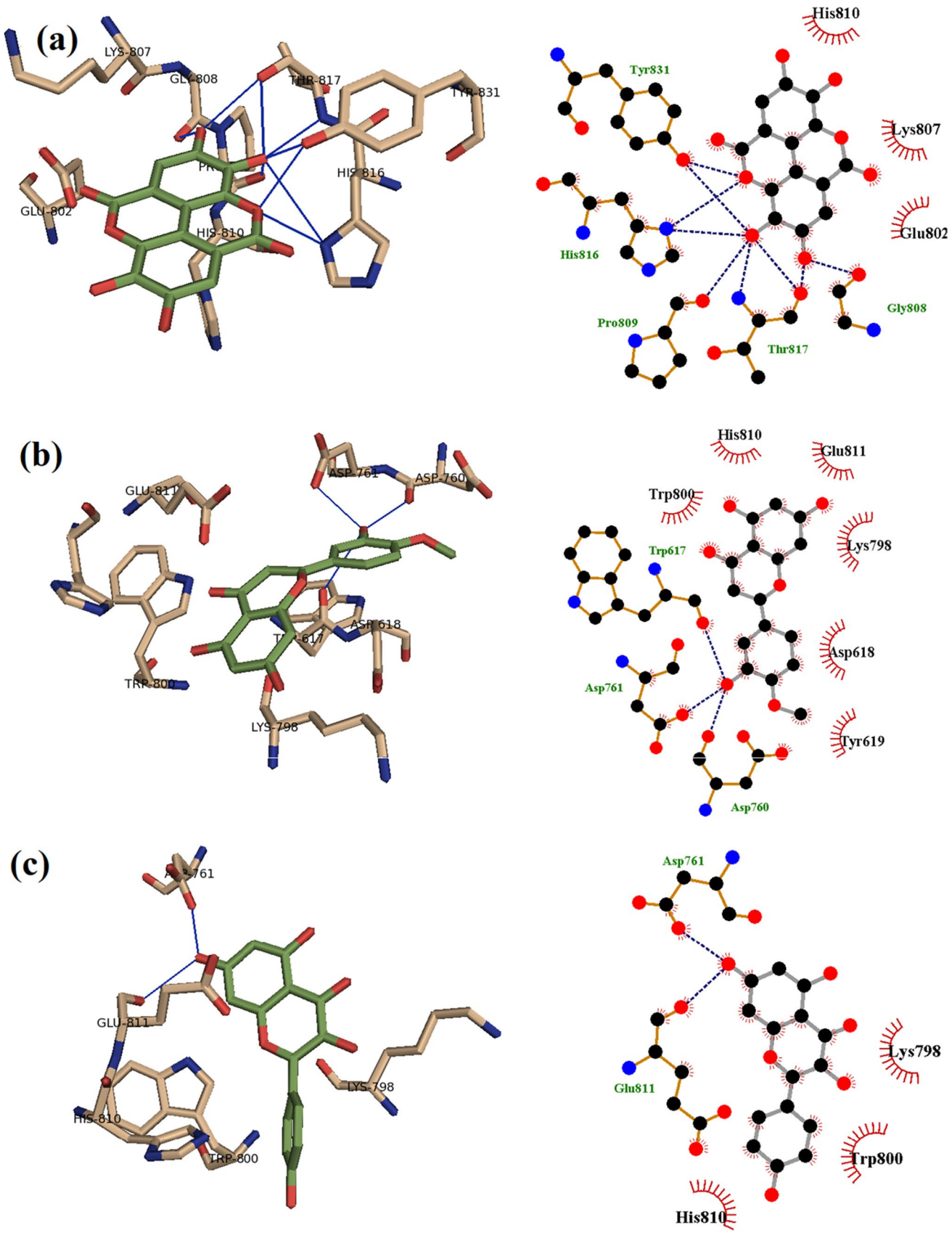


Fig. 4 Binding of (**a**) ellagic acid, (**b**) hesperetin, and (**c**) kaempferol with SARS-CoV-2 RNA-dependent RNA polymerase, highlighting explicit hydrogen bonds established. Reproduced from (Shaldam et al. 2021)

achieve further accuracy, it may be worthwhile to examine dynamic interactions between compounds and viral active sites using combined quantum mechanical and molecular mechanical (QM/MM) simulations. QM/MM and molecular dynamic simulations with accurate force fields would be an ideal approach in providing reliable information regarding the binding efficiency of compounds extracted from propolis to SARS-CoV-2.

Propolis and comorbidities in COVID-19 patients

Comorbidities are key points of attention in COVID-19 treatment regimes. The death of many patients with comorbidities were attributed to multiple organ failure, shock, acute respiratory distress syndrome, and arrhythmias. Nevertheless, special attention is required to help patients with comorbidities in the treatment of COVID-19 (Wang et al. 2020).

Potentially, propolis raises the tolerance against COVID-19, which causes an exaggerated inflammatory process especially in the lungs. For instance, patients having comorbidities including hypertension, chronic kidney disease, dyslipidemia, chronic lung disease, allergic rhinitis, carcinoma, cardiovascular disease, diabetes, obesity, liver disease, and malignant tumors lack the tolerance towards COVID-19 that significantly attribute towards high mortality rate (Korish and Arafa, 2011). Besides, the aging process brings to the fore many issues related to comorbidities and leads to a destabilized immune system with reduced tolerance towards diseases. Cardioprotective properties of propolis has been linked to the in vitro reduction of calcium ion concentration-induced oxidation of low-density lipoprotein (LDL) (Claus et al. 2000). Propolis extracts reduce the activity of activated macrophages and expression of the matrix metalloproteinase-9 (*MMP-9*) gene that is involved in extracellular matrix (ECM) protein degradation that plays role in the pathogenicity during atherosclerosis (Galis et al. 1994). Polyphenols in propolis exhibited an inhibitory effect against platelet aggregation, thus, anticoagulation activity (Zhang et al. 2017b). Further, the antihypertensive effect of propolis has been proposed through the reduced tyrosine hydroxylase activity, a feat that will eradicate the over-activation of the sympathetic nervous system (Gogebakan et al. 2012), and lessens oxidative stress via lower expression of malondialdehyde (MDA) (Selamoglu Talas 2014).

The effectiveness of propolis in treating pre-diabetic and diabetic patients was achieved by decreasing the blood uric acid levels (Fukuda et al. 2015), and improving the antioxidant status (Zhao et al. 2016; Gao et al. 2018). The effect of propolis in treating chronic kidney disease entails the significant reduction of proteinuria and the urinary level of the inflammation marker monocyte chemoattractant protein-1 (MCP-1) and high-sensitivity C-reactive protein (hs-CRP) (Silveira et al. 2019; Silveira et al. 2020). Considering these findings, the World Health Organization (WHO) reported that propolis can be used alongside key drugs or vaccine adjuncts to treat infections as a risk-free product (Berretta et al. 2020).

Propolis is also known as a natural blocker for PAKl, the vital facilitator of the inflammatory process instigated by COVID-19. Therefore, it reduces or somehow eliminates the overproduction of pro-inflammatory cytokines such as interleukin 6, interleukin 1, and tumor necrosis factor (IL-6, IL-1, and TNF). Naggar et al. proposed that breathing aerosolized propolis may help with the prophylaxis against seasonal allergies, asthma as well as the treatment of comorbidities including diabetes, cardiovascular diseases, and obesity—with the comorbidities being conditions that triggers to more severe difficulties within COVID-19 (Al Naggar et al. 2021).

Propolis has the potential to be vaccine adjuvant

The COVID-19 pandemic has renewed research interest in propolis products as a potential adjuvant for vaccines worldwide. Data from pre-clinical investigations of propolis in vitro and in vivo (Sforcin 2016) suggests that propolis aids immuno-regulation of pro-inflammatory cytokines, which as a result, reduce the risk of a "cytokine storm syndrome"—a major mortality factor in advanced COVID-19 infections (Bachiega et al. 2012; Bufalo et al. 2014). Some proof-of-concept experiments showed that propolis stimulates the generation of reactive oxygen species (ROS), as well as enhancing the fungicidal (Murad et al. 2002) and bactericidal (Orsi et al. 2005) activity of these cytokines cells. Thus, propolis also possesses the potential to activate the mechanisms utilized in killing microorganisms. Standardized propolis products with consistent bioactive components are now available and sold commercially. These products are extensively used in traditional herbal medicine and widely consumed as health and immune system boosters in many countries (Kuropatnicki et al. 2013; Silva-Carvalho et al. 2015). For example, numerous companies in Brazil produce and sell propolis products such as throat sprays and extracts.

Owing to its immunoregulatory potential, propolis has been considered as an ideal adjuvant for many candidate vaccines, including COVID-19 vaccines. To increase immunogenicity and ensure long-term protection of vaccines, vaccines must readily associate with selected adjuvants (El Ashry and Ahmad 2012). However, due to their reported toxicity and reactogenicity, all available adjuvants have one or more adverse effects in patients. Some of the adverse effects

include inflammation, pain, swelling, necrosis, ulcers, sterile abscesses, and systemic reactions such as nausea, pyrexia, allergy, eosinophilia, anaphylaxis, toxicity, adjuvant arthritis, and autoimmune diseases (Berretta et al. 2020). Ideal adjuvants should possess some ultimate characteristics such as being cost-effective, biodegradable, biologically inert, ability to boost cellular and humoral immune responses, and having a long shelf-life (Fan et al. 2015). Despite this, previous studies suggested considering the benefits of adjuvants and their adverse effects before use (Ma et al. 2011; Patel, 2016). New adjuvants have been approved for human use, but these require stricter regulation than those utilized in the veterinary field (Mojarab et al. 2020).

Since clinical investigations of propolis suggest that it possesses immunoregulatory, antiviral, and anti-inflammatory activities, it is therefore scientifically logical to also analyze propolis for the treatment of COVID-19 and as a potential adjuvant for COVID-19 vaccines. Adjuvant properties of propolis may enhance the individuals' immune response. The synergistic interactions between current antiviral drugs and propolis components should be clinically evaluated. We envisage that propolis may benefit COVID-19-vaccinated individuals by affecting cell entry, the viral life cycle, effecting an anti-inflammatory action, controlling the cytokine storm, and by boosting the production of antibody and cell-mediated immunity.

Limitations of using propolis

The limited number of reports and comparative studies that contain both biological activity and chemical composition of propolis from different climatic zones is a significant gap in propolis research (Katekhaye et al. 2019). Furthermore, propolis research and publications have been concentrated in a small number of countries. The majority of research has focused on propolis from Brazil and Europe. There have been, however, a few reports on propolis from Africa, New Zealand, and South Asia.

Further, the motivation for performing clinical trials frequently appears to be lacking or misdirected. This is most likely due to a lack of coordination among research initiatives as well as defined research objectives. The biological activities of propolis are being randomly tested by different research organizations, with little or no relevance to chemical composition. In addition, the small number of clinical studies is discouraging. Considering that propolis is recognized as having antibacterial properties in virtually all climatic zones, it is remarkable that so few clinical trials have been conducted. Propolis can reverse antibacterial resistance and lead to lower antibiotic doses through synergistic mechanisms, as well as reduce the likelihood of antibiotic resistance developing (Wojtyczka et al. 2013). These findings, however, must still be backed by clinical studies.

Another limitation in propolis research is inconsistencies in biological assessments. The antibacterial activity of propolis is the most essential of its many biological functions, especially in light of the growing problem of bacterial resistance to many treatments. Although the indicated findings in this review article are encouraging, the assessment approaches utilized in different studies vary greatly in terms of their concepts, analysis methods and research output. It is quite difficult to compare the outcomes of various procedures (Katekhaye et al. 2019). The antibacterial action of propolis is most typically measured using four approaches, namely, bio-autography, agar diffusion, agar dilution, and serial dilution assay (Seidel et al. 2008). Agar diffusion and bio-autography assays are typically presented as measurements in millimeters (mm), whereas broth dilution assays are published as minimum inhibition concentration (MIC) (Seidel et al. 2008). Aside from this fundamental difference, each approach has its own set of limitations. With propolis having a highly complex mixture of compounds with variable polarity, the diffusion method is not suitable for comparing propolis samples because results are directly influenced by the solubility of constituents in the agar media (Seidel et al. 2008). In addition, the choice of microorganisms to test against is also a challenge. Conclusion?

In today's era of modern techniques like liquid chromatography-evaporative light scattering detector (LC-ELSD), liquid chromatography-mass spectrometry (LC–MS/MS), liquid chromatography-nuclear magnetic resonance (LC-NMR), gas chromatography-mass spectrometry (GC–MS), high-performance thin-layer chromatographic (HPTLC), and other analytical techniques, it is difficult to apply a single standardized approach to propolis research due to the diverse chemical structures, molecular weight, and polarity of constituents (Katekhaye et al. 2019). This has led to inconsistencies in analytical investigations, and really, a limitation since it is technically challenging to combine data based on multiple analytical techniques and principles to detect certain types of biological components (Ni et al. 2007). For instance, the GC–MS reference library pool focuses on small-molecular-weight primary metabolites such as organic and aliphatic acids, sugars, and amino acids. LC–MS, on the other hand, can detect large, hydrophobic secondary metabolites including alkaloids, terpenoids, and phenols (Liu et al. 2017). Thus, when the total content of these constituents is reported and quantified using a reference library pool, there may be differences in the results from the two techniques. To overcome this constraint, the analysis of propolis based on a variety of approaches is necessary.

Future prospects (using nutraceuticals instead of pharmaceuticals)

Natural products, such as propolis, have long been employed as substitutes for pharmaceuticals in the medical field (Silva-Carvalho et al. 2015). Due to their synergistic effects, the complex mixture of propolis components may exude more health advantages than would be apparent by evaluating the individual impacts of components. The current method for approving pharmaceuticals has some limitations and these include the long lead time and significant expenditure required to discover new alternatives. In addition, time is also required to test pharmaceutical drugs for safety and effectiveness, and receive clearance for their usage after 5–10 years (Berretta et al. 2020). Potentially valuable material may never become available due to the enormous expenses required during this process and the likelihood that this lengthy procedure may not result in a product that will compensate for the investment required. Another issue is that modern medicine may be highly expensive. As a result, proper healthcare may not be available to everyone who requires it (Berretta et al. 2020).

Natural products can have numerous active ingredients, but modern pharmaceuticals typically have only one or a handful. Propolis, for example, contains hundreds of constituents (Berretta et al. 2020), many of which have the potential to help treat various forms of disease or have different mechanisms of action against a specific disease and its repercussions (de Mendonca et al. 2015). These potentials have not truly been investigated. According to Sadhana et al. (2017), Indian propolis has a high nutraceutical value and is free of pesticides and heavy metals. The propolis extract was standardized using an innovative high-performance thin-layer chromatographic (HPTLC) method that targeted markers including caffeic acid phenethyl ester, caffeic acid, galangin, luteolin, curcumin, apigenin, pinocembrin, and quercetin. Therefore, the indicated analytical approach can be used to screen propolis quality in the future.

Conclusion

The COVID-19 pandemic instigated by SARS-CoV-2 appears to be one of the deadliest that has occurred in the recent past. This pandemic is characterized by millions of human deaths and disrupted virtually all economic sectors across the globe. Preventive measures have been introduced worldwide to combat the spread of the SARS-CoV-2 virus along with special efforts dedicated to the swift production and provision of vaccines. However, vaccines are not universally accessible, and therefore, making it crucial to explore alternative options that can assist in reducing the spread of infections and COVID-19. To this end, some researchers are now advocating the use of a natural product known as propolis as part of the treatment regimen. Active compounds in propolis (including phenols, flavonoids, and terpenoids) are known to possess various pharmacological activities against various human diseases. Key among these functions are the antibacterial, antifungal, and antiviral properties. These properties are effected when active compounds interfere with, among other roles, viral entry into host cells and inhibit viral polymerase. The current study reviewed possible modes of propolis action when effecting various roles as well as being a possible adjunct in COVID-19 treatments. While special efforts are dedicated toward studying the properties of propolis in traditional medicine, further research is however still required to completely understand the underlying molecular mechanisms of propolis when inhibiting different microbes. It is currently predicted that the COVID-19 pandemic will last a few more years, and therefore, the use of alternative medicine including propolis may feature strongly in minimizing the spread of COVID-19 and act as an adjunct to treatment regimens.

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Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

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Conflict of interest The authors declare no competing interests.

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