Review Article

PROPOLIS: A POTENTIAL TREATMENT FOR COVID-19

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ABSTRACT:

The pandemic caused by SARS-CoV-2 and the disease it produces called COVID-19, necessitates the early search for therapeutic options. Propolis is considered a potential treatment mainly due to an inhibitory effect of PAK1, thus generating an immunomodulatory and anti-inflammatory effect. There is a potential antiviral effect of some abundant active ingredients in propolis, already evidenced in other coronaviruses. Recent data indicates a potential inhibitory interaction of the main protease of SARS-CoV-2 with the phenethyl ester of caffeic acid (CAPE) present in propolis, supporting a potential antiviral effect for treatment of COVID-19. Quercetin has also been postulated, due to several possible mechanisms of action and a proven inhibitory effect on SARS-CoV-1. Several propolis compounds have a potential blocking effect of the angiotensin converting enzyme (ACE II), the main receptor for SARS-CoV-2. Propolis has been administered in randomized clinical trials in other pathologies without reporting adverse effects. No negative interactions with conventional treatment for type 2 diabetes and chronic kidney disease were reported in randomized clinical trials. For these reasons, this article will review the pathophysiological considerations for the use of propolis in the treatment of the different phases of COVID-19, its potential benefit in association with vitamin D and C, and also propose a way of his administration.

Keywords: Coronavirus, COVID-19, treatment, antiviral.

INTRODUCTION

Propolis (propolis) is a natural balsamic and resinous product of bees [1]. Propolis is the product of the extraction of substances from plants by bees, to which salivary secretions and wax produced by the bees are added [2]. The composition of propolis is complex and more than 300 different substances have been identified in its composition. One of the reasons why the composition of propolis is variable is the variety of local plants close to the hive, from which the bees extract substances. The composition of propolis can

also vary according to altitude, lighting, food availability, species of bee and other factors. Polyphenols, mainly flavonoids and phenolic acids, are the main constituents of most propolis, with terpenes, aromatic substances, and beeswax usually less abundant [3]. There are geographical areas where local propolis have a particular concentration of terpenes, a characteristic example being the propolis from Santa Cruz (Camiri and Okinawa) and La Paz (Yungas) in Bolivia, which contrast with the rest of propolis rich in polyphenols from South America [4]. Propolis has been considered a potential treatment in multiple diseases due to its antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, antineoplastic, neuroprotective, cardioprotective (anti-atherogenic) effect, and stimulating wound regeneration [5]. The beneficial properties of propolis have been observed despite the variability of its composition, an example being the antimicrobial, anti-inflammatory and antineoplastic activity of propolis rich in terpenes [4, 6].

The disease caused by coronavirus 2019 (COVID-19) is caused by the new coronavirus called SARS-CoV-2. COVID-19 appeared in China in December 2019 as an emerging disease and has currently affected more than 200 countries, affecting more than 10 million people. COVID-19 has caused a marked increase in hospitalizations for pneumonia and systemic complications worldwide, as well as a significant number of deaths [7]. For these reasons, many studies are being conducted intensively to find treatments and vaccines with the aim of fighting COVID-19 [1]. Propolis is already considered a therapeutic option in COVID-19, both for its potential antiviral effects [8], as well as based on an anti-inflammatory and immunomodulatory effect as an inhibitor of the p21-activated kinase 1 (PAK1) pathway [9]. Propolis is a potential treatment for COVID-19 also because of its safety, low cost, and ease of use [1]. In this article we will carry out a descriptive review to justify its use in the different phases of COVID-19, as well as a dosage proposal for its administration.

COVID-19 PATHOPHYSIOLOGICAL CONSIDERATIONS

COVID-19 has 3 phases, during the first, called the early infection phase, the replication of the virus predominates. During the second phase, called the pulmonary phase, viral replication declines and the individual's inflammatory response becomes more active. The third, called the hyperinflammatory phase, is characterized by a predominant inflammatory response of the patient [10]. Angiotensin converting enzyme II (ACE 2) is a coronavirus receptor protein, and its activation produces increased PAK1 activity [11]. Spike protein activation is mediated by serine transmembrane protease 2 (TMPRSS2), for these reasons the SARS-CoV-2 cell input depends on ACE2 and TMPRSS2, and its blockade is a potential therapeutic target [12]. The blockade of PAK1 was associated with an increase in antiviral immune activity, particularly the production of antibodies, as well as the inhibition of pulmonary fibrosis [13], and an increase in the number of T and B lymphocytes [14]. For these reasons, the use of PAK1 blockers for the treatment of COVID-19 is considered a potential strategy [9].

THE SAFETY OF PROPOLIS USE IN CLINICAL AND PRECLINICAL STUDIES

Orally administered propolis was used in several randomized placebo-controlled clinical trials, without reporting adverse events. [15-20]. Randomized clinical trials with propolis range from the treatment of dysmenorrhea [15], to the treatment in diabetic patients with improved glycemic, lipid [16-17] and antioxidant profile [17], and even prolonged therapy of up to one year in patients with chronic kidney disease producing improvement in proteinuria [18]. In this sense,

the first point to consider in its safety is the absence of complications or pharmacological interactions reported when propolis is combined with conventional treatment for type 2 diabetes and chronic kidney disease [16-18]. The clinical trial in chronic kidney disease included patients with hypertension and no adverse effects were evidenced with the combined use of propolis and conventional antihypertensive treatment, nor were increases in blood pressure recorded [18]. The second point to consider is the absence of kidney and liver injury due to prolonged use of propolis in the elderly, evidenced in a 24-month randomized placebo-controlled clinical trial in the elderly with monitoring of liver injury markers and kidney function [19]. The third point to consider is that in animal models doses of up to 380mg/Kg/day are considered safe even during pregnancy [21]. Benefits have been reported in pregnancy results and placental oxidative stress in diabetic rats with doses of 300 mg/Kg/day [22], highlighting that these doses are more than 10 times higher than those used in randomized clinical trials in humans. In animal models a dose of 1400 mg/Kg/day is considered a safe dose [23]. The main adverse reactions reported are allergic, and to a lesser extent gastrointestinal [24]. These data demonstrate a very acceptable good safety profile for propolis for clinical trials in COVID-19, including in the elderly, people with comorbidities such as hypertension, diabetes, and chronic kidney disease, as well as a very theoretical safety profile acceptable for use in pregnant women.

TREATMENT IN THE VIRAL PHASE

Propolis has polyphenols, among these, kaempferol and chrysin show inhibitory activity on coronavirus in *in vitro* studies [8, 25]. Furthermore, quercetin and derivatives have shown *in vitro* inhibitory activity on the main protease in SARS-CoV-1 and MERS-CoV [6, 26]. In the case of SARS-CoV-2, using computerized molecular interaction prediction models, phenethyl caffeic acid ester (CAPE) is considered a potential inhibitor of the main SARS-CoV-2 protease with a degree of affinity comparable to that of protease inhibitor N3, which has already demonstrated an inhibitory effect on SARS-CoV-2 in an *in vitro* model [27]. CAPE mainly, and secondarily quercetin, kaempferol and chrysin would be the main candidate active principles as antivirals in the treatment of SARS-CoV-2 infection, with protease inhibition being the main probable mechanism of action [8, 25-27]. Inhibition of the SARS-CoV-2 protease is already a therapeutic strategy that has shown benefits in clinical trials with lopinavir/ritonavir [28]. Quercetin has already been considered as a potential treatment for SARS-CoV-2, and its possible mechanisms of action would have an inhibitory effect on the viral polymerase, an effect already demonstrated in other RNA viruses [29]. Several constituents of propolis have shown the ability to block angiotensin-converting enzyme II (ACE2) [30] and the kaempferol reduces the expression of TMPRSS2 [31], and these could be potential mechanisms for inhibiting the entry of SARS-CoV-2 into the cell. A study of the effect of propolis *in vivo* in animals demonstrated that a dose of 10 mg/Kg/dose has an antiviral effect comparable to a dose of 1 mg/Kg/dose of oseltamivir for the treatment of infection by the influenza virus [32]. The daily dose of oseltamivir adjusted by weight is 6 mg/Kg/day [33], so a probable antiviral dose of propolis is 60 mg/Kg/day. Based on the above, we consider treatment with propolis as promising in the early infection phase, where viral replication predominates, which would also support its use in the lung phase due to the significant presence of viral replication.

TREATMENT IN THE PULMONARY PHASE AND THE HYPERINFLAMMATORY PHASE

Propolis has been shown to have an anti-inflammatory effect by reducing levels of interleukin 6 (IL-6) and tumor necrosis factor

alpha (TNF-α) in randomized clinical trials [20]. CAPE has an *in vitro* inhibitory effect on the PAK1 pathway with consequent anti-inflammatory effect and inhibitor of pulmonary apoptosis [34], this effect is already considered as an option for the treatment of COVID-19, considering that it also has an immunomodulatory effect that stimulates the response immune, because PAK1 is an inhibitor of the individual's immune response [9]. The inhibitory activity of PAK1 has also been observed with other polyphenols present in propolis such as artepilin C (ARC) [35], being a characteristic (PAK1 inhibiting substances) that all propolis possess without exception [9]. The treatment of pancreatic cancer and type 1 and 2 neurofibromatosis with PAK1 inhibitors is already a reality, based on the neoplastic effect of PAK1 [9, 36-37]. Considering that the recommended dose to achieve this inhibitory effect of PAK1 is 250 mg/10Kg/day [9], this dose can be extrapolated to achieve the inhibitory effect of PAK1 in the treatment of COVID-19. The doses obtained with this scheme would be close to the doses used safely and in a controlled way in diabetic patients and even in patients with a high body weight, for which it would still be well below a dose considered safe in pregnant animals (380mg/Kg/day) [21].

COMBINATION TREATMENT OF PROPOLIS WITH VITAMIN D3 AND VITAMIN C

The PAK1 inhibitory effect of propolis would favor the activity of vitamin D3, because the increased activity of PAK1 increases the expression of the enzyme cytochrome P450C24 (CYP24) generating a consequent greater inactivation of vitamin D3 [9, 38]. Low levels of vitamin D have been correlated with worse outcomes in COVID-19 [39-40], however vitamin D3 treatment in COVID-19 is still controversial. It has already been considered that the failures in the clinical use of Vitamin D3 can be partly attributed to the inactivating effect of CYP24 [9]. For this reason the use of Vitamin D3 with propolis, at "PAK-1 inhibitory doses", offers a potential benefit. The combined treatment of Vitamin C and quercetin has already been considered as potential for the treatment of SARS-CoV-2 infection, due to a synergistic effect that favors the maintenance of serum levels of quercetin [29].

RECOMMENDATIONS

The probable mechanisms of action of propolis are summarized in figure 1. The treatment of the inflammatory state, based on the pathophysiology of the disease in the pulmonary and hyperinflammatory phases, has an acceptable safety profile and potential benefit, considering that propolis is already used as a PAK-1 inhibitor. It is necessary to start clinical studies in COVID-19 patients without the need to wait for *in vitro* studies of antiviral activity, due to the lower viral replication in these phases, and the greater pathophysiological contribution of the inflammatory state. The use in the early infection phase is justified by the described antiviral potential and safety profile. Thus, a dose of 25 to 60 mg/Kg/day is proposed orally divided into 3 doses for all phases of the disease, due to the antecedent of the dose of 25mg/Kg/day to obtain the inhibitory effect of PAK- 1 [2], the antecedent of antiviral activity in vivo at doses of 60 mg/Kg/day [24] and the antecedent of division into three doses in the randomized clinical trial in diabetics [9-10]. For dosing in the early infection phase, the proposed dose should be readjusted in the future according to variables such as the mean inhibitory concentration (IC50), which may be obtained in future *in vitro* studies. It is necessary to carry out clinical studies in patients with COVID-19, based on the safety profile and the potential benefit in all phases of the disease, and *in vitro* studies must also be carried out that add support to the theoretical antiviral effect for initial phases of the disease. It is necessary to determine the proportion of the main active principles of propolis that is

used in each clinical study in order to carry out studies with the active principles separately in the future that allow to elucidate their roles in the evolution of COVID-19.

CONCLUSIONS

The treatment of COVID-19 with propolis has pathophysiological bases and has an acceptable safety profile for all phases of COVID-19, supported by a potential antiviral effect and a confirmed anti-inflammatory and inhibitory effect of PAK1. Administration of propolis in conjunction with vitamin D and Vitamin C is a potential treatment option. It is necessary to start clinical trials in COVID-19 patients to show a real benefit.

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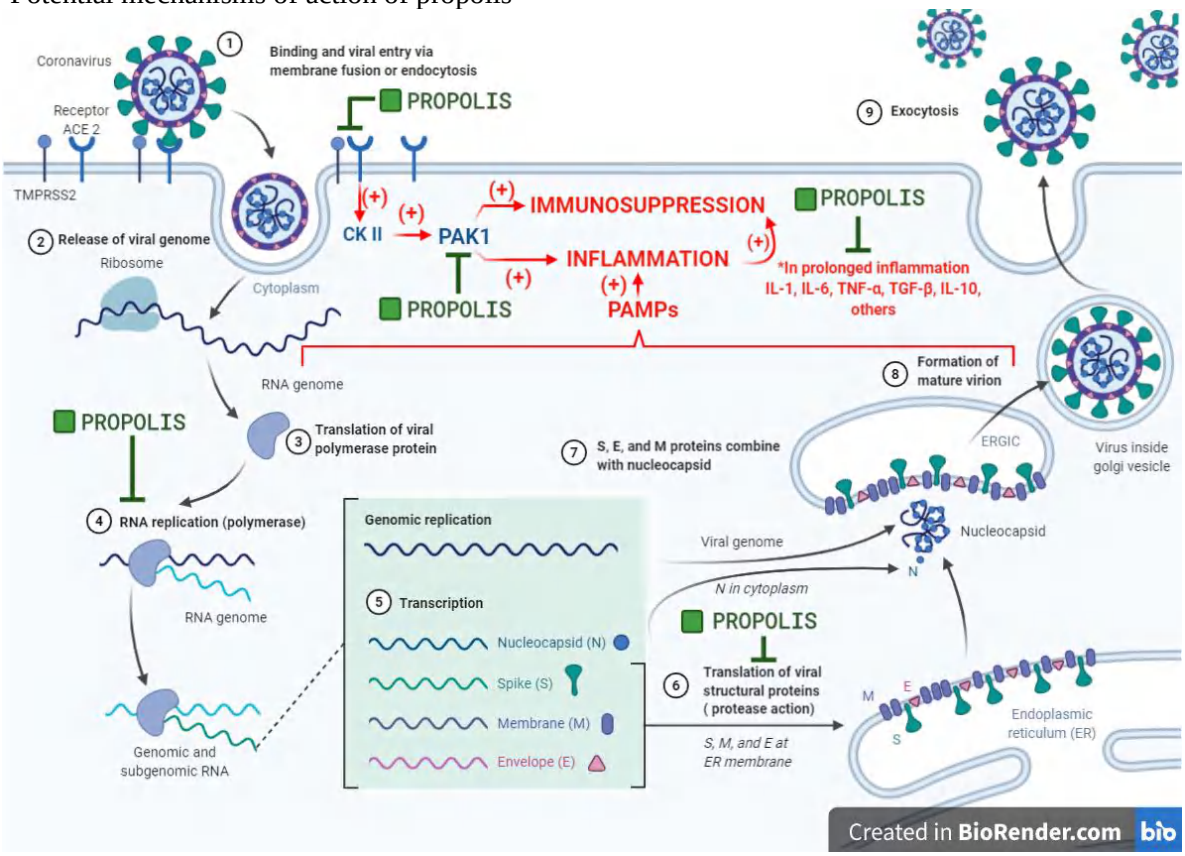
Figures

1. Potential mechanisms of action of propolis



Casein kinase II (CK II), angiotensin converting enzyme II (ACE 2), transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 10 (IL-10), p-21 activated kinase (PAK1), pathogens associated molecular patterns (PAMPs), serine transmembrane protease 2 (TMPRSS2). Created with BioRender.com