ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 10, pp. 41067-41069, October, 2020
https://doi.org/10.37118/ijdr.20132.10.2020

RESEARCH ARTICLE OPEN ACCESS

PROPOLIS AND ITS COMPONENTS CAN HELP REDUCE THE PHYSIOPATHOLOGICAL CONSEQUENCES OF COVID-19 INFECTION

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ARTICLE INFO

Article History:
Received 28th July, 2020
Received in revised form
01st August, 2020
Accepted 14th September, 2020
Published online 24th October, 2020

Key Words:
Pandemic, Sars-Cov-2, Propolis, Immune System, PAK1, ACE II, Infection.

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ABSTRACT

Many researchers and scientists have studied the new Coronavirus strain, COVID-19, searching of possible vaccines and treatments. Natural products have been widely used as an adjuvant treatment to prevent and relieve diseases, as they are generally inexpensive, widely available, rarely have adverse side effects and some have proven antiviral activity. It's in this bias that propolis and its components appear as potential candidates for materials that can help to reduce the pathophysiological consequences of COVID-19 infection due to its antiviral, antimicrobial, antitumor, anti-inflammatory, anesthetic, healing, antioxidant activities and immunity enhancer. Thus, propolis emerges as an alternative in the fight against the new coronavirus, by acting on the virus entry pathways in the host cell, both in the fusion of the viral envelope with the cell membrane, through the viral protein spike and the cell receptor ACE II, as in the endosome pathway, by blocking PAK1, a protein that mediates the process of micropinocytosis. In addition, propolis has an important role in the combat against opportunistic bacterial infection and in the strengthening of the immune system. Despite its limited production, propolis can be a great ally in the fight against coronavirus due to the positive impact of its pharmacological properties. For this reason, further studies related to the standardization of propolis and dosage must be carried out, as well as the increase of its production, since it is considered beneficial for the human species.

Citation: ***Giselle Sousa Carmona, Isabella Louise Morais de Sousa, RogérioValois Laurentino, Dalberto Lucianelli Junior et al.*** "Propolis and its components can help reduce the physiopathological consequences of covid-19 infection*", International Journal of Development Research*, 10, (10), 41067-41069.

INTRODUCTION

In the last few years, coronaviruses were responsible for two episodes of major pandemics. Initially, the (SARS) CoV in 2020 and the (MERS) CoV in 2012 (de Campos Tuñas *et al*., 2020; SBI, 2020). The SARS epidemy emerged in Hong Kong in 2003, and the Middle East Respiratory Syndrome (mers) emerged in the Saudi Arabia in 2012 (Lana *et al*., 2020). In December 2019, a set of pneumonia cases caused by a new strain of Coronavirusnamed COVID-19, began in the city of Wuhan, Hubei's province, China. The first available data about the new Coronavirus report high infection capacity, however, relatively low lethality (de Campos Tuñas *et al*., 2020; SBI, 2020). The high transmissibility of the virus contributes to high case rates and deaths by COVID-19. This infectious disease presents itself with different clinical aspects ranging from cases with few symptoms to others of high severity such as severe acute respiratory syndrome, thus presenting complex challenges for health, economy and society as a whole(Hu *et al*., 2020).Currently, COVID-19 is a public health emergency of international interest, as declared in January 30th, 2012 by the World Health Organization. In September 9th, 2020, there was more than 27 million confirmed cases of COVID-19 in more than 200 countries and more than 898 thousand deaths. The first COVID-19 confirmed case in Brazil was announced in February 26th 2020. In the current situation, the number of cases exceeds 4 million and the number of victims totals more than 127 thousand, making Brazil the third country with more cases and deaths by COVID-19 (Brasil, 2020; WHO, 2020). The transmission among humans occurs by direct contact or direct with mouth, eyes or nose membranes. The superior respiratory tract mucosae are the first line of defense, not only as physical barrier, but also through multiple innate and adaptive immune mechanisms that are crucial for the efficient antiviral responses (Docea *et al*., 2020). Regarding the humoral type of adaptive immune mechanism, there are evidence that such immune response does not last long after the established infection. Despite of this, the antibodies of some recovered patients, mainly the IgG type, specific against some parts of the virus, resist long enough for the utilization of the plasma from these COVID-19 recovered patients may show good results in the treatment of subjects with the disease (SBI, 2020). Natural products that historically being largely used to treat and avoid diseases are among the considered options of an adjuvant treatment for the COVID-19 infection, because they are usually not expensive, available and rarely present adverse reactions and some have proven antiviral activity(Berretta *et al*., 2020). Researches have shown that the propolis is highly beneficial for the human species and currently several pharmacological activities of phenolic acids and flavonoids are attributed to propolis, acting with several functional properties, such as antiviral, antimicrobial, antitumor, anti-inflammatory, anesthetic, healing, antioxidant and increased immunity activities(Kurek-Górecka *et al*., 2020). Regarding COVID-19 infection, the propolis have some important particular properties, such as the strengthening of the immune system and the reduction of the viral replication (Berretta *et al*., 2020). Propolis is a complex paste-like mixture formed by resinous and balsamic materials of plant origin, which is collected by bees and modified through their salivary secretions. The bees use propolis to repair cracks and damage to the hive, which helps in the maintenance of microorganisms. This fact served as an inspiration to the word propolis in Greek, which means, "in the defense of the city" or "in the defense of the hive" (Lustosa *et al*., 2008). It is in this context that the propolis and its components come as potential candidates to materials that can help reduce the pathophysiological consequences of COVID-19 infection.

LITERATURE REVIEW

A cell infection by an enveloped virus may happen by two process: virion fusion with the plasmatic membraneor by endocytosis followed by fusion of the virion with the endosome membrane, both processes involve the fusion of the virus with the cell membrane, both in the plasma membrane and in the membrane of the endosomal vesicle(Carter *et al*., 2007). The SARS-CoV-2 viral particle has lipids and S glycoproteins, also known as spike proteinin its viral envelope, this protein is responsible for the binding of the virus to its cell receptor generating the fusion mechanism with the cell membrane and therefore the entry of the virus in the host cell. The receptor for this S glycoprotein is an enzyme called ACE II (angiotensin II converting enzyme), which is found with greater expression in the lung, so one of the main symptoms is respiratory (Chen *et al*., 2020). Thus, the inhibition of the ACE II is an important target for the treatment against COVID-19infection (Sanchis-Gomar *et al*., 2020; Vardhan & Sahoo, 2020).Güler *et al*. (2020) found that the propolis component, a rutin, contains binding energy with an ACE II, Osés *et al*. (2020) evaluated several types of propolis for various characteristics, including the ACE inhibition, they found strong ACE inhibition for most types of propolis they studied, with ACE inhibition greater than 90%, the best results were found with the propolis' components: catechin and p-cumaric acid. The endosomal entry way of the virus in the host cell happens occurs through micropinocytosis, which is a type of endocytosis, morphologically defined by the presence of membrane extensions of actin external polymerizations called membrane fold. The folds of the membrane nonspecifically surround and internalize the fluid load in large vesicles or macropinosomes(Hansen & Nichols, 2009; Kerr & Teasdale, 2009), it is observed that the coronavirus explore a type of endocytosis, the micropinocytosisto gain entry into cells, this process being dependent on PAK1 activity(Burkard *et al*., 2014; Freeman *et al*., 2014). In this sense, cyclic AMP-dependent protein kinase (PAK1) is an important class of mediators of cell signaling that is involved in numerous signaling pathways responsible for biological responses that are relevant to the viral multiplication cycle (Bokoch, 2003; MANSER, 2005). Many viruses have already been shown to be able to usurp the PAK1 pathway to promote viral replication (Pacheco & Chernoff, 2010; Van den Broeke *et al*., 2010), such as Myxoma virus that requires PAK1 activation for a complete and efficient viral replication (Johnston *et al*., 2003). Among the possible targets to control the damage of COVID-19, the main "pathogenic" kinase PAK1 is the key (Berretta *et al*., 2020), the targeting of PAK1 to prevent macropinocytosis has been implicated for therapeutic intervention (Zhou & Simmons, 2012), thus, PAK1 inhibitors can be valuable for the treatment of COVID-19 infection. Among PAK1 blockers, there is caffeic acid (CA) and its ester (caffeic acid phenethyl ester = CAPE) found in the propolis, which are the first natural ingredients that have been shown to inhibit PAK1 (Zaki *et al*., 2012).

There are many evidences of the propolis and its compounds interfering in viral infectivity and replication, potentially diminishing the pulmonary inflammation due to its anti-inflammatory properties, while promoting the strengthening of the immune system, these are useful properties that can help to minimize the symptoms and deleterious effects of COVID-19 (Berretta *et al*., 2020). In a COVID-19 infection, the PAK1, a critical mediator in the cytokine storm, is super expressed in the lung, this frequently results in the mortality of hospitalized patients (Maruta & Kittaka, 2020).Although the mechanisms of action are not well understood, the components of propolis have potential as complementary supplements in the preventive treatment of chronic inflammatory diseases (Tőzsér & Benkő, 2016). According to Machado *et al*. (2012), in animal tests, the results showed that the group of rats that suffered induction of acute pulmonary inflammation by instillation of lipopolysaccharide and that received propolis extracts showed anti-inflammatory properties by inhibiting pro-inflammatory cytokines and by increasing anti-inflammatory cytokines suggesting an immunomodulatory activity of propolis, this group showed a reduction in the secretion of IL-6 and TNF-*α(pro-inflammatory cytokines) and increase in TGF-β*and IL-10 (anti-inflammatory cytokines), which may explain the inflammation inhibition observed.

The bacterial infection is a common complication in patients with COVID-19 (Wang *et al*., 2020). De Campos *et al*. (2020) showed that the main mechanism of action of propolis in bacterial cells is the disruption and lysis of these cells. In this sense, in addition to direct action on COVID-19, propolis is an important ally in combating opportunistic bacterial infections.
Propolis has been extensively tested as a vaccine adjuvant, because in addition to inducing an earlier immune response, it provides a longer protection period (Fan *et al*., 2015). The flavonoids present in propolis have potential as adjuvants, potentiating IgG, IL-4 and Interferon-γ (IFN-γ) in serum (Tao *et al*., 2014), which are elements that trigger immune

responses against pathogens. According to studies by Fernandes *et al*. (2015), propolis has a positive adjuvant effect on vaccines developed against canine coronavirus, these studies tested IFN-γ, which is an effective way to measure the cellular response induced by a vaccine; propolis also improved humoral and cellular responses in mice inoculated with inactivated virus vaccines (Fischer *et al*., 2010). Despite considerable evidence that propolis can reduce and relieve the symptoms of COVID-19, its acceptance as a health-promoting supplement in human medicine has been limited in many countries, because propolis products are not standardized because their components vary. This is because the composition of propolis varies with the plant species available in each region, and from which bees collect resins to produce it (Bankova, 2005; Toreti *et al*., 2013; Miguel *et al*., 2014). In this sense, minimum standardization is necessary to guarantee the effectiveness of this product, although the standardization of bee products is not yet a normal procedure, this reality already exists in the Phytopharmaceutical industry, Berretta *et al*. (2020) developed a Standardized Propolis Extract, called EPP-AF® (Patent Letter No. 0405483-0, approved by Revista da Propriedade Industrial on July 23, 2019), showing that clinical data support dosages of 375-500 mg of propolis / day, the dosage of 500 mg equivalent to 30 drops of propolis extract (with 11% weight / volume of dry matter), diluted in about 100 ml of water, or 3 to 4 units / day of capsules or tablets with the equivalent amount of extract. However, in cases of high severity of COVID-19, dosages above 500 mg / day could be used safely, as shown by the work of Soroy *et al*. (2014), indicating that 1200 mg / day is considered safe.

Conclusions and final Considerations

Thus, propolis emerges as an alternative in the fight against the new coronavirus, because it acts in the pathways of entry of the virus in the host cell, both in the fusion of the viral envelope with the cell membrane, through the viral protein spike and the cell receptor ACE II and in the endosomal pathway blocking PAK1, protein responsible for mediating the micropinocytosis process. In addition,propolis has an special role against opportunistic bacterial infections and in the strengthening of the immune system. Despite its limited production, propolis can be a great ally in the fight against coronavirus due to the positive impact of its pharmacological properties. For this reason, further studies related to the propolis standardization and dosage should be carried out, as well as the increase of its production, since it is considered beneficial for the human species.

Acknowledgements

We would like to thank the members of the Federal University of Pará, Altamira Campus, the Faculty of Medicine (FAMED) and the Study and Research Group on Health and Education in the Amazon (GEPSEA) for their collaboration.

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