

Propolis as an adjunct to prevention and treatment of radiotherapy- and chemotherapy-induced oral mucositis

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Abstract

Oral cancer is one of the eleven most prevalent cancers in the world. Treatment is surgery associated to radiotherapy and/or chemotherapy, although, therapy side effects deeply affect patients' life quality. Oral mucositis is the most frequent and uncomfortable side effect, and severe cases can cause treatment interruption and hamper disease control. There is no effective treatment against oral mucositis, thus, natural medicine is a promising source of effective substances when conventional treatment failed or selected resistant bacterial strains. Propolis is a natural substance available on pharmaceutical market. This research aimed to evaluate scientific publications concerning propolis anti-inflammatory activity, as well as its anti-bacterial action against oral flora micro-organisms, and to evaluate propolis employability as an adjunct to prevention and treatment of radiotherapy- and chemotherapy-induced oral mucositis. Propolis potential against oral mucositis is due to the association between its antifungal, antibacterial and antiviral properties, besides, its healing, antiulcer and anti-inflammatory activities.

Introduction

Oral cancer is one of the eleven most prevalent cancers among world population, approximately 150,000 people die of oral cancer per year and its incidence increased in the last years [1,2]. Treatment of choice is surgery associated to radiotherapy and/or chemotherapy [3], which is efficient in early stages of the disease, although, side effects deeply affect patients' quality of life.

Mucositis is considered the most severe non-hematological complication of cancer treatment. Extreme cases can interrupt treatment and hamper disease control [5,6]. Mucositis symptoms include severe pain, spontaneous bleeding, and mastication, swallowing and speaking difficulties; it is considered the most debilitating acute reaction of oral cancer treatment [4,7]. Mucositis etiology is associated to epithelial cells death, resulting in an atrophic epithelium and exposing connective tissue to opportunist microorganism's invasion normally present in the mouth, especially *Candida albicans* [4].

There is no effective treatment to oral mucositis [8]. Therapies aim to moderate painful symptoms through analgesics, accurate oral hygiene in order to induce selective decontamination and decrease opportunist infections, immunomodulatory drugs, growth factors, laser therapies, cryotherapy etc. Symptoms completely disappear with radiotherapy and chemotherapy conclusion [6].

Natural medicine is a promising source of effective substances with antibacterial action when conventional treatment failed or selected resistant bacterial strains [9,10]. Most natural antibiotics have complex chemical structures important on specific interactions, and are more easily recognized by pathogenic bacteria macromolecules targets. In addition, organisms from new ecosystems are frequently associated to a new chemical diversity, thus, pharmaceutical industry resumed researches on new antibiotics of natural origins [11].

Propolis is a natural substance alternative available on pharmaceutical market. It is a complex, non-toxic resin, collected by bees from tree buds, flowers and plants exudate, it has antibacterial,

antifungal, antiviral, anti-inflammatory, liver-protecting properties, besides, antitumour, immunomodulatory and healing activities, among others [12,13]. This biological potential results from synergism between propolis compounds, enhancing their effects. Studies confirm propolis synergic activity associated to antibiotics against bacterial strains resistant to benzylpenicillin, tetracycline and erythromycin. In conclusion, propolis synergic action is relevant and represents an effective alternative to synthetic antibiotics [12,14,15].

This research aimed to evaluate scientific publications concerning propolis anti-inflammatory activity, as well as its anti-bacterial action against oral flora micro-organisms, and to evaluate propolis employability as an adjunct to prevention and treatment of radiotherapy- and chemotherapy-induced oral mucositis.

Propolis chemical composition and biological activity

Pharmaceutical laboratories commonly use natural products as a rich, promising and alternative medication source. Propolis has attracted scientific attention, due to its multiple pharmacological properties related to its chemical composition. Various studies *in-vitro* and *in-vivo* aimed to characterize and comprehend propolis bioactivities and its isolated compounds, as well as to evaluate and validate its therapeutic potential [16].

Propolis is found worldwide, and its singular chemical composition is related to climate, local flora diversity and bee specie in order to define its physical, chemical and biological properties [15,17]. Three

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hundred compounds are responsible for these properties, which indicate propolis great chemical diversity and difficult standardization [18].

Phenolic compounds are currently found among isolated compounds of propolis samples collected from different locations on earth [19-23], especially flavonoids, isoflavonoids, phenolic acids, caffeic, and aromatic compounds [13,24], responsible for antibacterial, anti-inflammatory, antioxidant, antiviral, antifungal, and anticarcinogenic actions [25-27].

Caffeic acid phenethyl ester (CAPE) is a propolis' important active compound, which possesses anti-inflammatory and immunomodulatory properties. It is a potent and specific inhibitor of nuclear transcription factor NF-kappa B (NF-κB) activation, that regulates expression of genes related to immunological and inflammatory responses, which can provide molecular basis of propolis' anti-inflammatory and immunomodulatory activities [28,29]. Bufalo *et al.* [30] suggest that propolis anti-inflammatory effects are related to inhibition of nitric oxide production (inflammatory mediator) within macrophages. According to Paulino *et al.* [31], propolis anti-inflammatory action is also related to selective inhibition of COX-2, promoted by phenolic compounds present in its composition.

Propolis antibacterial activity against Gram-positive and Gram-negative bacteria, yeasts, and bacteria resistant to antibiotics has been widely studied. Although, mechanism of action has not been entirely understood, researchers consider that specific compounds, such as rutin, quercetin and naringenin, are substantial for its antibacterial activity, increasing bacterial membrane permeability, and decreasing adenosine triphosphate (ATP) production and mechanisms of transport through membrane. Synergism between propolis and synthetic antibiotics increases its antibacterial effect. This activity is strictly related to polyphenols and flavonoids concentration present in studied samples [13].

Wound healing is another important therapeutic indication of propolis [32-35]. Barbosa *et al.* [36] revised scientific studies and emphasized propolis efficiency on wounds treatment, acting as a healing agent and natural antibiotic. In addition, they associated propolis properties to the method, extraction location and product concentration.

Studies demonstrated propolis capacity to promote keratinocytes proliferation, stimulation of glycosaminoglycan deposition on the wounds, and modification of chondroitin sulfate/dermatan structure. Propolis efficacy on second-degree burns healing process indicates that propolis promotes wounds debridement, collagen synthesis stimulation, and inflammation reduction. Propolis mechanism of action on wound healing process is controversial, although, evidences affirm the mechanism is mainly based on synergism between its compounds, and its antimicrobial and anti-inflammatory properties [13].

Propolis action on mucositis

Mucositis, inflammation and ulceration on oral mucosa, is an uncomfortable sequel of cancer treatment. Onset occurs during radiotherapy and/or chemotherapy, due to cellular division interference and non-differentiation of cancer cells, which rapidly divide themselves, from normal cells with the same growth pattern, such as oral mucosa. Failure on cells reposition promotes epithelial rupture, exposing connective tissue and favoring opportunist microorganisms invasion, which substantially exacerbates clinical status of mucositis [37,38].

According to Simões, Castro and Cazal [38], there is a correlation between oral mucositis lesions and colonization by candida. Authors affirm treatment decreases patients' defenses, interrupting oral microbiota balance, and increasing *Candida albicans* population. This fungus is present over 30% to 50% of population without prejudice to the host, although, candida can become pathogenic during immunity deficit conditions, exacerbating oral mucositis symptoms and becoming more resistant to conventional treatments.

Mucositis care is limited to preventive measures, pain control and patients nutrition, cure is obtained only on cancer treatment conclusion. Prevention and control methods of mucositis include laser therapy and drugs to quell opportunist infections [39,40]. Drugs normally used to treat candida infections are polyenes and azole derivatives. However, these medications have undesirable adverse reactions and toxicity, besides, resistant strains have been described in literature [41]. Propolis is a promising option available among natural products, it is a non-toxic substance in recommended therapeutic doses, and possesses synergic effect between its compounds and when associated to antibiotics [15].

Javadzadeh *et al.* [42] conducted a triple blind, randomized clinical trial in order to test a propolis 3% aqueous antiseptic in head and neck cancer patients suffering from radiotherapy-induced mucositis. Their findings indicate it is a safe and efficient product of prevention and treatment of radiotherapy- induced mucositis. Another study evaluated a mucoadhesive gel containing propolis 5% in 24 adults with cancer during radiotherapy. Patients used the gel one day before radiotherapy beginning and during two weeks after treatment conclusion. By the end of research, 20 patients did not developed mucositis, two developed oral mucositis Grade 1 (according to mucositis grading scale) and two developed mucositis Grade 2; candida infection was not detected among patients [43]. This result indicates propolis can reduce oral mucositis symptoms and prevent lesions occurrence.

Propolis reduced and detained radiation induced mucositis in rats [44]. Benderli and Deniz [45], noticed propolis was efficient to reduce mucositis severity in rats, and, in addition, rats treated with propolis had their biochemical and histopathological parameters normalized compared to group with isolated irradiation.

As mentioned before, radiotherapy- chemotherapy- induced epithelial alterations on oral mucosa are exacerbated due to oral microorganisms' invasion, mainly candida, thus, controlling this fungus is essential to relieve mucositis. Propolis antifungal activity over *Candida albicans* was verified by many researchers [46-51]. Freires *et al.* [51] considered propolis a promising substance for oral candidiasis treatment after observing the strong anti-candida activity of propolis samples used in their research.

Siqueira *et al.* [52] evaluated fungistatic and fungicidal activities of a Brazilian red propolis ethanolic extract, against different candida species compared to chlorhexidine, and using fluconazole as control. All candida species were susceptible to propolis and chlorhexidine, although, five samples of *C. albicans*, *C. tropicalis* and *C. glabrata* were resistant to fluconazole antifungal activity. Szweida *et al.* [47] also noticed in their research that propolis was active against fungus strains resistant to fluconazole, confirming Siqueira *et al.* results.

A similar investigation evaluated susceptibility of *Candida albicans* strains collected from HIV-positive patients to an ethanolic extract of propolis 20% and to some standard antifungal recommended to oral candidiasis treatment, such as nistatin, clotrimazole, econazole and

fluconazole. Results showed propolis and nistatin inhibited all *Candida albicans* strains and were significantly superior to other antifungals tested [53].

Propolis action on skin and mucosa wounds treatment has been investigated by researchers [32,33,41]. Kiderman *et al.* [54] case report of a one year old child affected by bilateral eosinophilic ulcers unsuccessfully treated with various products during four months. Definite cure could only be provided after lanolin-based propolis ointment application. According to authors, although circumstantial, the fact that propolis promoted wounds cure deserves further and more detailed studies concerning propolis healing properties. Pensin *et al.* [55] tested propolis against rats' oral mucosa ulcers, and noticed pain score diminish and wounds healing time reduction, similar to results obtained by Grégio *et al.* [56], Samet *et al.* [57] e Vieira *et al.* [58].

Conclusion

Propolis is a versatile drug and its great therapeutic potential has been widely studied by researchers over the world, although, it stills unknown by a considerable part of population. Therefore, this revision's findings are likely to be of great interest to health professionals and general population, concerning therapeutic indication of this peculiar drug. The number of scientific publications concerning propolis has substantially increased over the last years, and findings confirm this bee product efficiency and versatility. Propolis has antifungal, antibacterial and antiviral activities, besides anti-inflammatory and healing actions. Thus, propolis is able to assist prevention and softening of oral mucositis symptoms due to its wide biological effect, acting on all disease stages.

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