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Phytotherapy in Dentistry: A Literature Review Based on Clinical Data

Thaylla Núñez Amin Dick^{1*}, Letícia Côgo Marques¹, Amanda de Almeida Lima Lopes¹, Monique Santana Candreva¹, Lílian Rocha Santos¹ and Bruna Lavinas Sayed Picciani¹

¹Universidade Federal Fluminense, R. Marquês de Paraná, 303 – Centro, Niterói – RJ, 24033-900, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. Authors TNAD, BLSP conceived the study. Authors TNAD, LCM, AALL, MSC participated in the data collection and interpretation, drafting and review. Author LRS managed data interpretation and review. Author BLSP providing inputs on its draft, review and final approval. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Looking for scientific support with an updated review about herbal medicines usage in dentistry for clinical application, reinforcing the potential of phytotherapics to treat oral disorders and the need for new studies on the topic.

Material and Methods: The literature search was performed combining "phytotherapy" and "dentistry" in the PubMed, MEDLINE, BBO, LILACS and SciELO databases, covering the period from January 2017 to March 2020. The data extracted were: Alteration/oral disease, gender, age, number of participants, herbal medicine used, drug function and results.

Results: were selected 24 papers that employed different plants, such as Tulsi, *Aloe vera*, citronella, turmeric, propolis and cloves. The results found are promising and show the anti-inflammatory, analgesic, antibacterial, antioxidant, antifungal, antiviral and tranquilizer action of herbal drugs, and their use for treating burning mouth syndrome, oral submucous fibrosis, xerostomia and halitosis.

*Corresponding author: E-mail: thayllanunez@gmail.com;

Conclusion: despite the therapeutic activities of herbal medicines, additional studies with larger sample size and scientific rigor are necessary to prove their benefits for treating oral diseases.

Keywords: Phytotherapy; dentistry; oral manifestations; medicinal plants.

1. INTRODUCTION

Herbal medicines are active substances produced with plants and popularly used as an effective alternative for treating several ailments, oral diseases includina [1]. Currently. approximately 40% of the available medicines use natural sources, directly or indirectly, 25% of which are obtained from plants [2]. Research on herbal medicines in dentistry has been expanded in the search for new alternatives that combine analgesic, antiinflammatory, antimicrobial, curativeand regenerative activity. with toxicity, less better biocompatibility and more affordable costs [3,4].

Morales-Bozo et al. [5] evaluated the effectiveness of a salivary substitute based on chamomile and flaxseed for treating xerostomia. Milani et al. [6] associated cognitive therapy with chamomile tea to treat patients diagnosed with burning mouth syndrome, concluding that there was an increase in well-being, maintenance of oral moisture and confidence in the therapeutic approach proposed. In 2019, Salehi et al. [4] reviewed works on plant-derived bioactives in the oral mucosa, citing the benefits of Aloe vera in regenerating tissue and increasing cell proliferation quickly and effectively: besides its anti-inflammatory, immunomodulatory, analgesic, bacteriostatic, bactericidal and antioxidant effects. The authors also cited green tea acting on chronic periodontitis activity, anti-caries and anti-fungal (candidiasis), reducing the adverse effects of conventional drugs, culminating in less fungal resistance [4]. The World Health Organization (WHO) also recommended and encouraged using plants as a tool for oral hygiene [7]. However, the role of herbal drugs in controlling oral changes is still undervalued when compared to other diseases, such as skin diseases [8]. Thus, this study is a narrative review that aimed scientific support about herbal medicines usage in dentistry for clinical application, reinforcing the potential of phytotherapics to treat oral disorders and the need for new studies on the topic.

2. MATERIALS AND METHODS

2.1 Search Strategies

Literature search performed combining "phytotherapy" and "dentistry", after previously identifying the chosen descriptors in articles published on the topic and in the Medical Subject Headings (MeSH). The PubMed, MEDLINE, BBO, LILACS and SciELO databases were accessed covering the period from January 2017 to March 2020.

2.2 Inclusion and Exclusion Criteria

English-language publications with the title and abstract related to the topic were included. Incomplete articles, duplicated ones, studies on animals, and those that, when read, did not fit the proposed theme were excluded from the research.

2.3 Analysis

From the selected articles, *in vivo* or *in vitro*, the following information were extracted: oral alteration/disease, gender, age, number of participants, herbal medicine used, drug function and results. From the literature reviews, only the mentioned herbal medicines, their function, and the conclusion of the study.

3. RESULTS

The search resulted in 79 published papers, with 31 potentially eligible identified after applying the inclusion and exclusion criteria. Then reading these papers in full, 24 studies remained: 17 original studies, 01 case report, 02 systematic reviews and 04 literature reviews (Fig. 1).

The results found are promising and show the anti-inflammatory, analgesic, antibacterial, antioxidant, antifungal and antiviral action of herbal medicines, and their use for treating burning mouth syndrome, oral submucous fibrosis, xerostomia and halitosis (Table 1). These studies use several plants, such as Tulsi, *Aloe vera*, citronella, turmeric, propolis and cloves.

Author, Year	TS	Evaluation	no.	Gender	Age	Herbal medicine	Result
De Souza et al. [9]	LR	Burning mouth	7 studies	-	-	Catuama, capsaicin 0.02%, chamomile gel, urea 10%, spray containing lycopene- enriched virgin olive oil (300ppm), <i>Aloe vera</i> 70% and <i>Hypericum perforatum</i> extract 300 mg	Significant improvement observed in catuama and capsaicin 0.02% oral rinse when compared with placebo. The others reported effectiveness in symptom reduction, but without statistical difference when compared with the placebo/control groups.
Resende et al. [10]	LR	Repair, regeneration, proliferation, mineralization, wound healing, and induced differentiation	35 studies (In vitro)	-	-	Propolis, Cocos nucifera, Aloe vera, Cammelia sinensis, Punica granatum, Nigella sativa, Ricinus communis, Croton lechleri, Marmosa rubra, Salvia officinalis, Capparis spinose, Curcuma longa and soy milk	The plants showed potential effect on cell viability and proliferation. The articles evaluated mainly the action of plants on cells of the periodontal ligament. Propolis, coconut water and <i>Aloe vera</i> were the most common storage medium.
Santi et al. [11]	LR	Dental plaque and gingival inflammation in patients with gingivitis	-	-	-	Camelia sinensis, Azadirachta indica, Anacardium occidentale Linn, Schinus terebinthifolius and Curcuma longa	Five herbal products showed better results than chlorhexidine in dental plaque and gingival inflammation reductions.
Moro et al. [12]	LR	Chronic periodontitis	7 papers	-	-	Aloe vera gel, 10% Emblica officinalis gel, bark of Mimusops elengi, bark of Acacia arabica and seeds of Punica granatum, Garcinia mangostana gel, Centella asiatica (1.4 and 1.9) and Punica granatum (0.2 and 0.3) extracts.	In systemically healthy patients with periodontitis, the local use of phytotherapics as adjuncts to scaling and root planning may have additional benefits in the reduction of probing pocket depth and clinical attachment level gain, when compared with scaling and root planning alone.
Al-Maweri et al. [13]	SR	Submucous fibrosis	6	-	-	Aloe Vera	Aloe vera may be effective in managing submucous fibrosis, without any side effects.

Table 1. Data found in the studies

Author, Year	TS	Evaluation	no.	Gender	Age	Herbal medicine	Result
Aumeeruddy et al.[14]	SR	Phytochemistry, pharmacological properties, and bio- applications	Not reported	-	-	Salvadora persica L.	Salvadora persica L. showed a wide scope of application and its uses extended beyond the traditional uses of its roots, stems, and twigs in oral care.
Dantas et al. [15]	OS	Control of anxiety in patients undergoing dental extraction	40 patients	27 F (67,5%) / 13 M (32,5)	Youn ger than 18 years	Passiflora incarnata	Passiflora incarnata showed an anxiolytic effect similar to midazolam, and was safe and effective for conscious sedation in adult patients who underwent extraction of their mandibular third molars.
Patri & Sahu [16]	OS	Cavity Disinfectant Adjuncts in Minimally Invasive Dentistry	40/ divided into four groups	-	-	Tea tree oil and Aloe vera	Natural antibacterial agents like tea tree oil and <i>Aloe vera</i> could be effectively used as cavity disinfectants which will help in minimizing secondary caries and rendering a long term restorative success.
Wiatrak et al. [17]	OS	Hygienic agent and Periodontal health.	37	54% F/ 46% M	41- 82 years	Ethanolic extract of propolis and tea tree oil.	Improvements in hygiene and the condition of periodontium were observed in patients using toothpastes with ethanolic extract of propolis and tea tree oil. No influence on the reduction of denture plaque and influence on microorganism's composition in oral microflora.
Purohit et al.[18]	OS	Pulpotomymedicament in primary teeth	50	-	4-9 years	Turmeric	Pulpotomy treatment using turmeric powder in primary teeth has shown good clinical and radiographic success.
Lolayekar & Kadlkhodayan, [19]	OS	Change in salivary pH and viability of S. mutans	30 patients	Not reported	9 to 12 years	Ocimum sanctum	Ocimum sanctum has an antimicrobial effect on S. mutans present in the saliva, without causing any known systemic side

Author, Year	TS	Evaluation	no.	Gender	Age	Herbal medicine	Result
							effects and chewing of <i>Ocimum</i> sanctum leaves has no significant effect on the salivary pH levels.
Ferreira-Filho et al. [20]	OS	Caries	3	Not reported	5.67 years	<i>Bauhinia forficata</i> Link	Antimicrobial and mechanism to inhibit tooth demineralization of <i>Bauhinia forficata</i> Link.
Dar-Odeh et al. [8]	OS	Oral diseases among female patients	232 patients	100% F	18 to 69 years	Most of the natural remedies used (n = 17) were herbal, with cloves (71.1%) and <i>Salvadora</i> <i>persica</i> (26.7%)	Majority of patients use natural remedies to treat their oral disease. Patients were mostly satisfied with natural remedies in terms of effectiveness and lack of complications
Albabtain et al. [7]	OS	Dental plaque, sub- gingival microbiota, and gingival inflammation	28	57% F	18 to 71 years	Salvadora persica L.	There were no significant differences in the microflora after using active and inactive Salvadorapersica.
Milani et al. [6]	CR	Burning mouth	2	100% F	59 and 68 years	<i>Matricaria recutita</i> (Camomile)	Psychological treatment along with <i>Matricaria recutita</i> phytotherapy displayed excellent results in the control of BMS.
Isola et al. [21]	OS	Surgical removal of impacted mandibular third molar	82	53% M	26.8 years	Herbal medicine: composed of baicalin (<i>Scutellaria baicalensis</i> <i>Georgi</i>) 190 mg; bromelain (<i>Ananas comosus</i>) 50 mg; aescin (<i>Aesculus</i> <i>hyppocastanum</i>) 30 mg	The herbal mixture of herbal extract with anti-inflammatory activity has shown to be safe and simple in controlling post-surgical discomfort after surgical removal of the third molar. There were favorable effects on the inflammatory process parameters.
Lee et al. [22]	OS	Periodontal disease	In vitro	-	-	Terminalia chebula	<i>Terminalia chebula</i> may be a beneficial supplement to help prevent dental plaque bacteria-mediated periodontal disease.
Silva et al. [23]	OS	Antifungal Activity	In vitro	-	-	Chrysobalanus icaco	Chrysobalanus icaco was shown to possess antifungal activity

Author, Year	TS	Evaluation	no.	Gender	Age	Herbal medicine	Result
							against Candida species with clinical importance in the development of oral candidiasis, and these activities may be related to its chemical composition.
Tonea et al. [24]	OS	Antibacterial and antifungal properties	In vitro	-	-	Mix extract between <i>Arctium</i> <i>lappa</i> root powder and <i>Aloe</i> <i>barbadensis</i> Miller gel, Amoxicillin with clavulanic acid and Fluconazole (as control substances)	The experimental mix extract of <i>Arctium lappa</i> root powder and <i>Aloe vera</i> gel is able to inhibit very resistant microorganisms, like <i>Enterococcus faecalis</i> and <i>Candida albicans</i> .
Veloso et al. [25]	OS	Potential antibacterial and anti-halitosis activity	In vitro	-	-	Caesalpinia ferrea Mart, Cinnamomum cassia B., Mallow sylvestris L., Punica granatum L., Rosmarinus officinalis, Aeolanthus suaveolens, Sysygium aromaticum L. and Tamarindus indica L.	The extracts displayed antimicrobial activity against the tested microorganisms. The investigated plants have the potential to reduce the main substances related to halitosis of oral origin.
Guandalini Cunha et al. [26]	OS	Evaluation of cytotoxicity and antimicrobial efficacy	In vitro	-	-	Cymbopogon nardus	Citronella oil and alcohol-free chlorhexidine completely inhibited the growth of S. aureus and C. <i>albicans</i> biofilms in the adhesion phase. All solutions showed inhibitory activity against 24h biofilm formation. However, citronella led to greater microbial reduction and presented the lowest cytotoxic effect.
Da Silva et al. [27]	OS	Antibacterial and Cytotoxic Activities	In vitro	-	-	P. elliottii e P. tropicalis	Data reveal the in vitro antibacterial activity of the <i>P.</i> <i>elliottii</i> and <i>P. tropicalis</i> resins against cariogenic bacteria in the planktonic and in the sessile modes.

Author, Year	TS	Evaluation	no.	Gender	Age	Herbal medicine	Result	
De Araújo et al. [1]	OS	Caries	In vitro	-	-	Anacardium occidentale L. and Anadenanthera macrocarpa	Anacardium occidentale extract has potential as an antimicrobial agent with low eukaryotic cell toxicity or mutagenic activity. Anadenanthera macrocarpa extract, although absent of antibacterial activity might be a safe and effective phytotherapeutic alternative.	
Teodoro et al. [28]	OS	Antifungal activity	In vitro	-	-	Buchenavia tomentosa	The Acetone fraction presented the best antifungal activity among several extracts from <i>Buchenavia</i> <i>tomentosa</i> .	
(*)Type of Study (TS); Literature review (LR); Systematic review (SR); Original studies (OS); Case reports (CR)								



Fig. 1. Flowchart of the selection and result of the papers

4. DISCUSSION

Ancient practice, the use of herbal agents has been increasingly investigated with greater scientific rigor to confirm its beneficial effects [9]. The main reason for more controlled studies is that differences in the cultivation, harvesting, processing and storage of the leaves result in a considerable change in the amount of therapeutic constituents, which can influence the final effect of the drug [19]. However, the studies found in the literature show promising results and effects in the herbal medicines usage in Dentistry.

Lolayekar & Kadkhodayan [19] evaluated the effect of chewing Tulsi leaves (*Ocimum sanctum* – "holy basil") on salivary pH and viability of *S. mutans*, considered one of the factors for the development of tooth decay – which changes the pH of the biofilm resulting in the demineralization of the tooth surface – in children aged 9 to 12

years. The study confirmed the antimicrobial effect of the plant in S. mutans and the absence of side effects, but without changes in salivary pH. In 2020, Ferreira-Filho et al. [20] also studied the antimicrobial and dental demineralization effect in vitro, using the tincture of Bauhinia forficate Link, popularly known in Brazil as "cow's foot". The study aimed to evaluate initial Streptococcus spp. total count of microorganisms and the final superficial microhardness of the tooth [20]. The authors concluded that, despite the limitations of in vitro work, the tincture of B. forficata L. is a potential substance against caries, due to its antimicrobial activity in mature biofilm and possible inhibitory mechanism of tooth demineralization [20]. Patri & Sahu [16] compared the efficacy of herbal antibacterial agents - Tea tree oil and Aloe vera with commercially available 2% chlorhexidine as cavity disinfectant for use in minimally invasive dentistry. They found that natural antibacterial agents could be effectively used as cavity disinfectants, which will help in minimizing secondary caries and rendering a long-term restorative success. Aside from Tulsi, Tea tree oil and *Aloe vera* and tincture of *B. forficata* L., using chamomile to control dental plaque and treat gingivitis has been studied and proven [6]; propolis also showed an anti-inflammatory effect in osteogenic differentiation and bacterial growth reduction, maintaining the viability of oral cells [10].

Aloe vera, Cymbopogon citratus, Quercus brantii, Coriandrum sativum, Mimusops elengi, Acacia arabica showed anti-inflammatory, antibacterial and antioxidant properties, which may help control gingivitis and periodontal disease. [29-32]. The topical use of herbal medicines, allows for greater concentrations of active agents for long periods in periodontal pockets, which act as a regular drug storage [30] Treatment with the ethanol extract of Terminalia chebula inhibits the growth of dental plaque bacteria (DPB) as well as DPB-induced inflammation, and effectively DPB-lipopolysaccharides-induced abolishes osteoclastic bone resorption in vitro. It is an effective botanical chemopreventive agent that can modulate DPB-induced inflammatory factors involved in gingivitis and periodontal disease[22].

Santi et al. [11] stated in their literature review that, in the studies found, herbal mouthwashes achieved significant reductions in dental plaque and gingival inflammation when compared with placebo rinses. Five products based on Camelia Azadirachta indica, Anacardium sinensis, occidentale Linn, Schinus terebinthifolius and Curcuma longa showed better results than chlorhexidine in reducing dental plaque and gingival inflammation. However, they cautioned that the majority of randomized controlled trials included in the review did not reach definitive conclusions [11], and the need for further studies to better assess the effect and clinical relevance of natural mouthwashes on gingival inflammation and biofilm control [11]. Already, Wiatrak et al. [17] investigated the influence of a propolis and tea tree oil-containing hygienic agent on selected oral health parameters, oral microflora and the condition of periodontal health. They concluded that toothpaste with active ingredients improved hygiene and the condition of periodontium demonstrated the beneficial influence on microorganisms composition in oral microflora [17].

Regarding fungal infections, *Candida albicans* is a versatile microorganism that, under certain

systemic conditions. can cause oral complications such as candidiasis and especially mucositis. in older. diabetic or immunocompromised patients [26]. Traditional antifungal drugs, such as azoles, amphotericin B and echinocandin are generally used to treat candidiasis [33]; but the limited number of antifungal agents and misuse of the available drugs resulted in many cases of resistance to treatment [33]. Thus, natural products are promising alternatives for solvina these infections, presenting less toxicity and significant antimicrobial activity [34].

Tonea et al. [24] compared the antibacterial and antifungal properties of different endodontic products, two commercially available, one experimental plant based extract and two control substances. The disc diffusion assay was used to determine the antibacterial and antifungal properties of chlorhexidine, calcium hydroxide, a mix extract between Arctium lappa root powder and Aloe barbadensis Miller gel, Amoxicillin with clavulanic acid and Fluconazole (as control [24]. substances) And, as result. the experimental mix extract of Arctium lappa root powder and Aloe vera gel was able to inhibit very resistant microorganisms, like Enterococcus faecalis and Candida albicans [24]. A new idea of using powdered turmeric as a material of pulpotomy procedure in primary teeth showed good clinical and radiographic success [18]. In this study, with 50 children aged between 4 and 9 years, who were having carious unilateral or bilateral deciduous molar in maxillary and mandibular arch, Purohit et al. [18] fixed the pulp stumps with the mixture of turmeric powder distilled water and radiopague material with the help of cement carrier. In the observation after 3 weeks, 2, 4, and 6 months follow-up, only one patient (6.66%) reported pain after 6 months and none of the patients reported tenderness, mobility, and sinus/ fistula after 6 months [18]. Silva et al. [27] investigated the antibacterial activity of two resins of the genus Pinus and of an isolated compound, the dehydroabietic acid (DHA).This diterpene study was the first that has verified the P. tropicalis resins exhibit significant antibacterial activity against cariogenic bacteria. Besides that, assessment of the antibiofilm activity of DHA against endodontic bacteria revealed results and prevented significant all the bacteria from forming a biofilm. Regarding cytotoxicity, all the promising concentrations the resins were below the cytotoxic of concentrations [27].

Considering the need for new methods to help control biofilm, aiming for maximum antimicrobial and antifungal efficacy with minimal side effects, Guandalini et al. [26] studied the effectiveness of two solutions based on citronella oil in biofilms formed by S. aureus and C. albicans, compared with two commercial rinses without alcohol, one based on 0.12% chlorhexidine (Periogard) and the other with essential oils (LT, Listerine Zero). The authors concluded that citronella-based compounds had a greater anti-biofilm effect when compared with commercial solutions. regarding S. aureus and C. albicans. Considering the concentrations of active ingredients in commercial mouthwashes, citronella showed less cytotoxic effect [26], appearing as an active phytocomplex with antimicrobial and antifungal action, viable for creating a new mouthwash to help control biofilm.

Salvadora persica L. (S. persica), considered an important medicinal plant with bioactive compounds and several pharmacological properties, appears as an alternative for treating oral diseases [7,14]. The main antimicrobial of S. persica is benzyl isocyanate (BITC), an antiviral against Herpes simplex, which inhibits the growth and production of acids by Streptococcus mutans and is fungistatic for Candida albicans. However, it is highly volatile and rapidly evaporates from the oral cavity [7,14]. Buchenavia tomentosa and Chrysobalanus icaco, natural plants from central Brazil, showed promising antifungal activity for Candida albicans, reducing its ability to form biofilms, hyphae and adhere to oral epithelial cells [23,35,36]. Just like cloves, used since antiquity to relieve dental pain and to treat oral candidiasis and herpes infections [8].

Burning mouth syndrome-a condition characterized by burning or pain symptoms, especially in the tongue, lips, hard and soft palate, without clinical signs - is managed by numerous treatments: Drugs, laser therapy, acupuncture, and psychological counseling. Aside from traditional therapies, chamomile (Matricaria recutita) has shown satisfactory results in maintaining oral moisture, with no reported adverse effects [6], as well as catuama and 0.02% capsaicin rinse, suggesting that these therapies should be studied in greater depth [9]. However, this syndrome requires the patients' psychological characteristics assessment, not just the treatment employed [9].

Another disease that includes pain/burning sensation is oral submucous fibrosis, a debilitating chronic disease with a high risk of

Dick et al.; EJMP, 31(10): 1-13, 2020; Article no.EJMP.57992

malignant transformation: pain/burning, vesicle formation, hypomobility of the hard palate and tonque, loss of taste and sensitivity, intolerance spicy foods, speech and swallowing to problemsand severe limitation on mouth opening. Hence, a recent study employed Aloe vera as a alternative for controlling natural the complications of this disease, for its several therapeutic benefits: analgesic, antiinflammatory, immunomodulatory, antioxidant, anti-neoplastic and wound regeneration actions. withoutno reported side effects. However, its effectiveness in controlling submucous fibrosis is still controversial [13].

Regarding the feeling of dry mouth and halitosis, the study by Dar-Odeh et al. [8] reported the use of olive oil for dry mouth and halitosis and tahini (sesame paste) for dry mouth and oral ulcers. Veloso et al. reported that pomegranate and jucá (*Libidibiaferrea*) can potentially combat microorganisms related to halitosis, as the studied extracts inhibited oral microorganisms that produce volatile sulfur compounds [25].

In relation to pain, numerous strategies have been developed to manage postoperative discomfort, such as the pharmacological approach, which inhibits the synthesis and/or release of mediators of acute inflammation. Corticosteroids and non-steroidal antiinflammatory drugs (NSAIDs) have shown immunosuppression. anti-inflammatory and analgesic effects [37]; but these cause a subsequent decrease in the renewal of serotonin in the central nervous system, leading to central inhibition prostaglandin, of resulting in undesirable adverse effects [38]. As an alternative to these medications, studies proposed natural substances such as bromelain, which has shown anti-inflammatory activity, mainly anti-edema action due to proteases present in its composition.

Isola et al. [21] proved the effectiveness of a herbal medicine composed of baicalin, 190 mg; bromelain, 50 mg; aescin, 30 mg. Baicalin has antibacterial [39], antiviral [40], anti-tumor [41] and anti-inflammatory properties [42], in addition to improving osteoblasts activity in bone formation [43] and negatively regulating inflammation pathways. Aescin showed antiinflammatory action with an anti-edematous effect through its antihistamine and antiserotonergic components, which reduces the adhesiveness and migration of neutrophils. The authors found a more favorable response to

Dick et al.; EJMP, 31(10): 1-13, 2020; Article no.EJMP.57992

postoperative pain, when compared with the placebo group and the group that received ibuprofen. However, reduction in facial edema and improvement in mouth opening was observed in the three groups, with no significant difference in the results after extraction of impacted lower third molars [21]. Already the cloves, has analgesic effect attributed to the activation of calcium and chloride channels in ganglion cells and the agonist activity of capsaicin [8]. However, natural drugs, when applied topically, can result in complications such as burns caused by garlic to relieve toothache [8].

Regarding to pre-surgical anxiety, Dantas et al. [15] compared the effects of *Passiflora incarnata* and midazolam for the control of anxiety in patients undergoing mandibular third molar extraction. *Passiflora incarnata* showed an anxiolytic effect similar to midazolam, and was safe and effective for conscious sedation in adult patients who underwent extraction of their mandibular third molars[17].

5. CONCLUSION

Although herbal medicines have been used since ancient times for treating oral diseases and have important therapeutic activities, such as anti-inflammatory, analgesic, antibacterial, antioxidant, antifungal, antiviral and tranquilizer actions, additional studies, with greater sample sizes and scientific rigor, are necessary for proving their benefits in treating oral diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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