

THE THERAPEUTIC USE OF TEA TREE AND COPAIFERA ESSENTIAL OILS IN ORAL REPAIR – A SYSTEMATIC REVIEW

O USO TERAPÊUTICO DOS ÓLEOS ESSENCIAIS DE TEA TREE E COPAIFERA NO REPARO ORAL – UMA REVISÃO SISTEMÁTICA

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RESUMO

Introdução: Nos últimos anos a busca por princípios ativos que ajudem no processo de cicatrização impulsionaram o uso de fitoterápicos. Os óleos essenciais apresentam diferentes propriedades, entre elas, efeitos anti-inflamatório, bactericida, antisséptico, analgésicas, hidratante e cicatrizante. No contexto da Odontologia, tem sido cada vez mais explorado o uso de óleos essenciais, pois estes podem contribuir positivamente para a recuperação do paciente. **Objetivo:** O objetivo dessa presente revisão integrativa foi identificar na literatura, estudos que avaliaram a eficácia dos óleos essenciais de Copaifera e Tea Tree como agentes reparadores de lesões orais. **Materiais e métodos:** Somente artigos científicos de caráter experimental disponíveis nos bancos de dados eletrônicos PubMed /Medline, Scielo, Cochrane e Bvsalud, foram selecionados. O período de pesquisa bibliográfica compreendeu os meses de outubro de 2021 a março de 2022. **Resultado:** A amostra constituiu-se de 5 artigos publicados entre os anos 2012 e 2022, sendo todos realizados em roedores. Quatro dos cinco estudos incluídos notificavam o potencial terapêutico de Copaifera e Tea Tree na cicatrização de feridas orais. **Conclusão:** Os OE representam uma alternativa terapêutica efetiva e de baixo custo para o manejo do processo de cicatrização, no entanto, torna-se necessário embasamento científico para

ampliação da prática de forma segura e eficaz.

Palavras- Chave: Óleos essenciais; Mucosa oral; Reparo oral; Mucosa bucal; Cicatrização de feridas.

ABSTRACT

Introduction: In recent years, the search for active ingredients that help in the healing process has boosted the use of herbal medicines. Essential oils have different properties, including anti-inflammatory, bactericidal, antiseptic, analgesic, moisturizing and healing effects. In the context of Dentistry, the use of essential oils has been increasingly explored, as they can positively contribute to the patient's recovery. **Objective:** The objective of this integrative review was to identify in the literature, studies that evaluated the effectiveness of Copaifera and Tea Tree essential oils as repairing agents for oral lesions. **Materials and Methods:** Only scientific articles of experimental nature available in PubMed/ Medline, Scielo, Cochrane and Bvsalud electronic databases were selected. The period of bibliographic research comprehended the months of October 2021 to March 2022. The sample consisted of 5 articles published between the years 2012 and 2022, all of which were carried out in rodents. **Results:** Four of the five included studies reported the therapeutic potential of Copaifera and Tea Tree in the healing of

oral wounds. **Conclusion:** EO represent an effective and low-cost therapeutic alternative for the management of the healing process, however, scientific basis is necessary to expand the practice in a safe and effective

way.

Keywords: Essential oils; Oral mucosa; Oral repair; Buccal mucosa; Wound healing.

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INTRODUCTION

Essential oils (EO's) represent a group of secondary substances extracted from selected plants that consist in complex sets of different terpenes and aromatic compounds, such as phenols and phenylpropanes. Most EO's can be obtained by different methods, for example: distillation. Others are mechanically pressed from plant tissues or can be extracted with solvents. It has been documented that in 3500 BC, in Ancient Egypt, EO's were used in the social context for religious, cosmetic and, above all, medicinal purposes. With maritime expansionism, knowledge about EO's grew in other countries, like China and India, becoming part of the Indian Ayurvedic medical system^[1]

Known all over the world for their medicinal, antiseptic, bactericidal, virucidal and fungicidal properties, and for their fragrances, EO's have been used over time in embalming processes, food preservation and as antimicrobial agents, analgesics, sedatives, healing, anti-inflammatory, spasmolytic and local anesthetics. The pharmaceutical use of EO's is becoming more widespread as an adjuvant alternative to the use of synthetic chemicals^[2].

In Brazil, policies for the use of medicinal plants and herbal medicines gained prominence from 1982 onwards, with the Medicinal Plant Research Program of the Central de Medicamentos (CEME). In 2008, phytotherapy was recognized and regulated as an integrative and complementary practice to Oral Health by the Federal Council of Dentistry, on November 19, 2008, by Resolution 082/2008- CFO. With the advancement of knowledge about

phytotherapy, the therapeutic potential of EO's has been increasingly documented. There is a wide variety of plants that can be used for medicinal purposes, and the pharmacological use of their EO's is of great relevance for the various areas of health, among which Dentistry stands out. Aleluia et al. (2015)^[3], reported that the antimicrobial, antifungal, anti-inflammatory, analgesic and aromatic properties of EO's can contribute to the resolution of lesions in the oral mucosa. In this perspective, the use of EO's by dentists may represent an effective alternative for the management of conditions of the bucomaxillofacial complex, although there is still a shortage of studies related to their therapeutic indication in Dentistry^[4]. It is important to highlight that the therapeutic properties of the EO's could contribute to the biomodulation of the cicatricial process of oral lesions and stimulate their quick resolution, since there is already evidence that proves the beneficial action of their active principles^[5].

In Alvarenga et al. (2020)^[6] study for example, the Copaifera oil was used for a clinical analysis of experimentally induced wounds on the ventral surface of the rat's tongues, and it was able to promote a significant early reduction in the area of the oral wound when compared to the other experimental groups. Similar results have already been reported in humans, as demonstrated by Scotti et al. (2018)^[7]. In this study, the authors reported promising effects of a bioadhesive gel containing a mixture of EO's, including Tea Tree essential oil, on oral mucosa wound healing and postoperative inflammation controlling. It was documented that one week after starting to use the gel, some surgical wounds already

showed partial or complete re-epithelialization, while the others showed stable fibrin clot.

Given the above, the aim of this systematic literature review was to document the effectiveness of two types of EO's widely used in Brazil – Tea Tree (Tea tree) e Copaifera (Copaifera). In particular, this study aimed to verify the applicability of these EO's as a therapeutic alternative, isolated or complementary to other biomodulatory therapies used in Dentistry, to stimulate the repair of oral mucosa wounds.

MATERIALS AND METHODS

2.1 Study design

This was a systematic review that was prepared according to the PRISMA methodology (Key Items for Reporting Systematic Reviews and Meta-analyses). This study was submitted to the PROSPERO platform, with registration number CRD42023376231 and aimed to answer the following central question: "Are the essential oils of Tea tree (Tea tree) e Copaifera (Copaifera) effective in repairing wounds in the oral mucosa?"

2.2 Search Strategy

Only scientific articles available in PubMed/Medline, Scielo, Cochrane e Bvsalud (BVS), electronic databases were selected. The period of bibliographic research comprised the months of October 2021 to March 2022. The following keywords were used as search descriptors ("essential oils" [MeSH Terms] OR "essential oils" [All Fields]) AND ("oral repair" [MeSH Terms] OR ("oral repair" [All Fields] AND "oral mucosa" [All Fields]) OR "oral mucosa" [All Fields] OR ("buccal" [All Fields] AND "mucosa" [All Fields]) OR "buccal mucosa" [All Fields] OR ("wound" [All Fields] AND "healing" [All Fields]) OR "wound healing" [All Fields]), used this way, in all banks of data. "Copaifera" and "Tea tree", and the boolean expression AND.

2.3 Eligibility Criteria

Inclusion criteria covered online articles classified as retrospective and prospective studies, with an in vivo experimental character only, published over a 10 year period, from 2012

to 2022. Only studies that reported the use of Copaifera and Tea Tree the on oral wound repair, were selected. Studies found in these data sources, that covered other essential oils, and such as literature reviews and clinical case reports were not included.

2.4 Data Extraction

The construction of the research question was carried out from the PICOS anagram (population, intervention, control, result and type of study, in which "P" represented animals with oral wounds in need of healing; "I" indicated the use of essential oils Copaifera and Tea tree in the oral wound repair as a therapeutic approach; "C" included animals that did not receive any type of treatment for oral wound, "O" represented the outcome of the study, namely, the oral wound, "S" represented the types of studies.

2.5 Data Synthesis Strategy

Information from the manuscripts about the year, type of study, population, results and outcome were inserted in a descriptive table.

The bibliographic search was carried out by I.P.S and B.C.L.M and the level of agreement between the examiners was measured using the Cohen kappa index and was 0.98.

RESULTS

Initially, 199 articles were found through a search in the specified databases: 142 in PubMed, 24 in BVS, 21 in Cochrane and 5 in Scielo. Furthermore, an active search was carried out for other studies cited in the references of the articles identified in the first bibliographic survey, which culminated in the inclusion of 7 more studies. In the screening process, 105 duplicate articles were excluded. About 89 studies were excluded after reading the titles and abstracts and 69 of these did not answer the central question, 8 were in vitro experimental studies and 12 were case reports. After these initial analyses, 12 articles were selected and considered eligible for full text reading and from this sample, 5 were included for broader discussion in the present study because they were related to the central question of this review.

Flowchart 1- Article search strategy according to the inclusion criteria. Search period: October 2021 to March 2022. Salvador, Bahia.

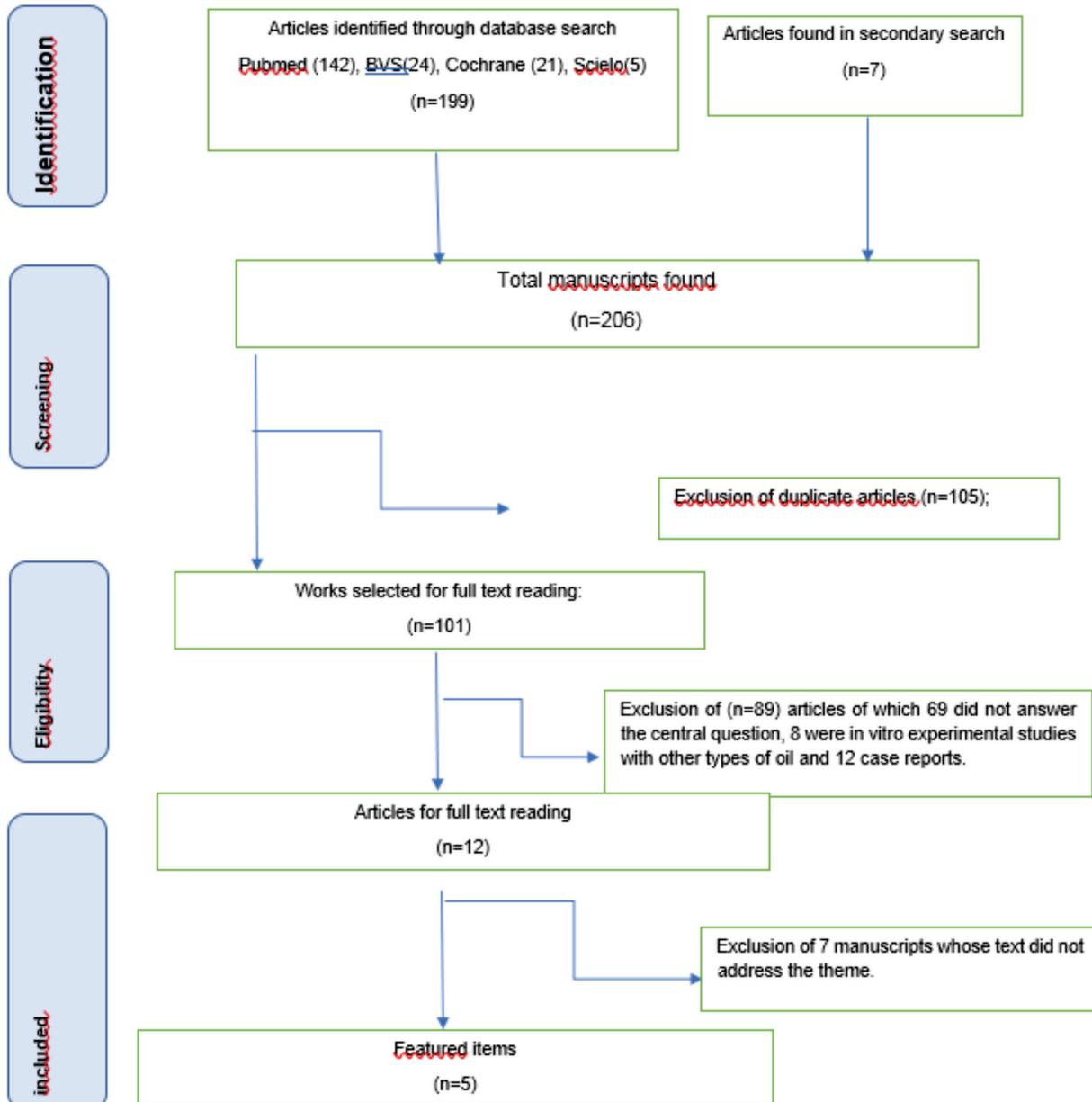


Table 1. Description of selected studies according to inclusion and exclusion criteria. Search period: October 2021 to March 2022. Salvador, Bahia.

Title	Journals Authors	Objective	Methodology	Results	Conclusion
Essential oil of <i>Tea tree alternifolia</i> for the treatment of oral candidiasis induced in an immunosuppressed mouse model	<i>Rasteiro et al., (2014)</i>	To determine the minimum concentration of <i>M. Alternifolia</i> necessary to eradicate <i>C. albicans</i> biofilms formed in vitro and to study the effects of this concentration in the treatment of induced oral candidiasis in an immunosuppressive mouse model.	(n=12) The minimum inhibitory concentration (MIC) and the minimum biofilm eradication concentration (MBEC) of <i>Tea tree alternifolia</i> were determined by microdilution assay. For the in vivo study, twelve immunosuppressed rats with oral candidiasis received topical applications of <i>M. alternifolia</i> with MBEC. After treatment, yeasts were collected from the rats and quantified (CFU/mL). Rats were sacrificed for morphological analysis of the dorsum of the tongue by optical and scanning electron microscopy. Data were analyzed using Student's t-test or the Mann-Whitney test.	The minimum inhibitory concentration of <i>Tea tree alternifolia</i> (MIC) was 0.195% and the minimum biofilm eradication concentration (MBEC) was 12.5%. Treatment with <i>Tea tree alternifolia</i> resulted in a reduction of 5.33 trunks in <i>Candida albicans</i> and reduced microscopic lesions of candidiasis.	<i>Tea tree alternifolia</i> oil at a concentration of 12.5% was effective in eradicating <i>C. albicans</i> biofilm and reducing <i>C. albicans</i> yeasts in a model with immunosuppressed mice.

Safety and Effectiveness of Copaiba Oleoresin (<i>C. reticulata Ducke</i>) on Inflammation and Tissue Repair of Oral Wounds in Rats	Alvarenga et al., (2020)	To investigate the therapeutic effects of <i>Copaifera</i> oleoresin (<i>C. reticulata Ducke</i>) on epithelialization and attenuation of the inflammatory response in an animal model of traumatic ulcer induced in the rat's tongues. To analyze the safety of the dosage used in this experiment through biochemical parameters of liver and kidney functions, in order to introduce oleoresin as an alternative therapy in oral lesions.	(n=45) A biopsy wound was induced in the tongue's ventral surface of forty -five male Wistar rats under anesthesia. The animals were randomly allocated into three experimental groups: Control, corticoid and <i>Copaifera</i> . A daily dose of each treatment and vehicle was administered by oral gavage for three consecutive days. Collections took place on the third, seventh and 15th days post -injury for clinical and histopathological analyzes. Blood was drawn on the 3rd and 7th for liver and kidney function tests. Semi-quantitative analyzes were performed based on inflammation and reepithelialization values. Tissue collagen deposition was detected by picosirius staining.	Wounds treated with <i>Copaifera</i> demonstrated a reduced wound area, a decrease in the acute inflammatory reaction and a greater degree of re-epithelialization. (p<0.05). Levels of kidney and liver function tests did not reveal the presence of post -treatment damage.	<i>Copaifera</i> oil-resin is a safe and effective alternative therapy for inflammation and tissue repair of oral wounds in this animal model.
Effects of Copaiba Oil Topical Administration on Oral Wound Healing	Wagner et al., (2020)	To evaluate the clinical and histopathological aspects regarding the treatment with <i>Copaifera</i> extract oil (<i>Copaifera Reticulata Duke</i>) on the healing of oral wounds through an animal model, in comparison with the topical treatment of corticosteroids.	(n=96) Traumatic ulcers were performed on the dorsal region of the rat's tongues using a 3 mm punch. The animals were divided into groups: Control, Corticosteroid, Placebo and <i>Copaifera</i> . The animals received two daily applications of the products. In this context, the Control group received only daily handling. Six rats in each group were euthanized on days 3, 5, 10 and 14. The percentage of repair was calculated and histopathological aspects were analyzed. The Kruskal-Wallis test was used to compare results between groups and	The corticosteroid group lost more weight on days 10 and 14 than the control group (p< 0.05). Furthermore, this group's healing time was longer than that of the Control group (p=0.007). No differences were observed between <i>Copaifera</i> and the Control group.	The results of the study suggest that topical administration of <i>Copaifera</i> oil (<i>Copaifera Reticulata Duke</i>) did not promote relevant side effects in this animal model and did not accelerate the process of healing of ulcers through the oral route.

The influence of topical and systemic administration of copaiba oil on the alveolar wound healing after tooth extraction in rats	Dias-da-silva et al., (2013)	To evaluate the influence of topical and systemic administration of Copaifera oil on alveolar wound healing after tooth extraction in rats.	(n=28) Molars and premolars of male Wistar rats were extracted. Subsequently, they were divided into four groups, according to the treatment performed: (a) alveolar irrigation with Copaifera oil; (b) alveolar irrigation; (c) daily washing with Copaifera oil or (d) daily washing with saline solution. After the sacrifice of the animals, the mandibles were removed and processed in order to obtain the decalcified histological sections.	The authors observed a high level of epithelial migration, a small number of inflammatory cells and vascular increase in animals that received systemic administration of Copaifera oil. (p<0.05). However, rats treated with topical administration showed ulcerations and high numbers of inflammatory cells. Increased vascular neoformation in bone was reported in both groups treated with Copaifera oil when compared to the placebo group. (p<0.05).	Topical or systemic administration of Copaifera oil effectively contributed to better alveolar bone healing. However, topical application to connective tissue must be considered carefully with regard to wound repair.
Copaiba oil -resin (Copaifera reticulata Ducke) modulates the inflammation in a model of injury to rat's tongues	Teixeira et al., (2017)	To evaluate the anti-inflammatory properties of Copaifera oil -resin (Copaifera reticulata Ducke) in a model that transfixes lesions on the rat's tongues.	(n=20) 5 male Wistar rats were submitted to the <i>Copaifera</i> oil-resin oral toxicity test in order to measure the therapeutic dose, which was established at 200 mg/kg/day. Then, a total of 15 new animals were submitted to transfixing injury and randomly divided into three groups based on treatment: Control, Dexamethasone and Copaifera oil -resin group. After 7 days, histological processing and staining with hematoxylin and EO'sin and immunohistochemistry for CD68 occurred. (Finally, the samples were analyzed using the Imaagem J cell counter.	The acute toxicity test showed that Copaifera oil-resin has low toxicity. In addition, the oil -resin from Copaifera showed significant results regarding the reduction of inflammatory response, chronic inflammatory infiltrate, and number of macrophages.(p<0.05).	Copaifera oil-resin has been shown to be effective in reducing the chronic inflammatory infiltrate and inhibiting macrophage activity. Furthermore, as it is not effective in reducing edema, the authors recommend further investigations that seek to elucidate the action of therapy with regard to the mechanism associated with inflammation.

DISCUSSION

This present systematic review aimed to verify if there is scientific evidence on the effectiveness of Tea tree and Copaifera essential oils in the oral wound repair, in particular, focus on experimental models in rats. This choice reflects during the bibliographical survey, a considerable number of manuscripts on the subject were found, most of it addressed the therapeutic use of these EO's in cutaneous healing, in isolation or in comparison to other types of oils. No experimental study was found that comparatively evaluated the effects of Tea tree and Copaifera oils on oral wound repair.

It is known that tissue repair is a tightly regulated event that aims to restore tissue after an injury, in order to provide a return to original function and morphology, whenever possible. Regardless of the type of tissue affected, the healing process follows four partially overlapping phases: hemostasis, inflammation, proliferation and remodeling [8]. During repair, potent chemical mediators are biosynthesized, including pro and anti-inflammatory cytokines, growth factors, reactive oxygen species, vasoactive amines, and plasma protein activation. There is a growing integration of these mediators with immunocompetent cells, leading to a consequent stimulation of the formation of a new extracellular matrix and proliferation of parenchymal cells [9].

Regarding the oral cavity, oral mucosa wounds heals faster and more efficiently than those on the skin, and several factors may contribute to this difference, including tissue morphology, vascularization and the presence of saliva [10]. However, oral mucosa healing can also represent a particular challenge, as it is an environment subjected to constant physical trauma and because it presents a complex ecosystem of microorganisms, which can stimulate the persistence of the inflammatory phase and the development of possible post-operative complications [11]. Bearing this premise, numerous biomodulatory therapies have been proposed, such as photobiomodulation, ozone therapy and, more recently, the use of EO's.

Teixeira et al. (2017) [12] documented the effectiveness of using Copaifera oil to accelerate the healing process through an experimental study with 15 Wistar rats. These

animals were randomly allocated into three groups that received different dosages, except for the control group. It was observed that Copaifera oil (*Copaifera reticulata* Ducke) can modulate the inflammatory process, decrease the recruitment of inflammatory cells and accelerate the healing process after 7 days of oral treatment. However, this result was similar to that found in animals treated with dexamethasone. The histological sections of the dexamethasone group showed a lower degree of edema, which did not occur in the control group or in the Copaifera group. None of the groups appeared to have fibrosis or necrosis. Although steroids have an advantage with regard to their action on edema, they have been associated with numerous local and systemic side effects [13].

Therefore, the use of other agents, such as Copaifera resin oil, which can reduce inflammation and accelerate cell repair without causing adverse effects, becomes a relevant, safe and comfortable alternative for the patient. The results of this study indicate that Copaifera oil-resin is a natural product that is effective in reducing the chronic inflammatory infiltrate and inhibiting macrophage activity. As it was not effective in reducing edema, the authors suggest further investigations that seek to elucidate the role of this oil on other mechanisms associated with inflammation. They have been associated with numerous local and systemic side effects [13]. Therefore, the use of other agents, such as Copaifera resin oil, which can reduce inflammation and accelerate cell repair without causing adverse effects, becomes a relevant, safe and comfortable alternative for the patient. The results of this study indicate that Copaifera oil-resin is a natural product that is effective in reducing the chronic inflammatory infiltrate and inhibiting macrophage activity. As it was not effective in reducing edema, the authors suggest further investigations that seek to elucidate the role of this oil on other mechanisms associated with inflammation.

Within this context, Alvarenga et al. (2020) [6] investigated the action of *Copaifera reticulata* Ducke oil through a study with 45 Wistar rats. A punch biopsy wound was induced on the ventral surface of the rat's tongues, which were separated into three groups based on treatment: control, corticosteroid and Copaifera. Copaifera oil was mixed with

saline solution and 5% Tween 20 to enable solubilization of the oil in serum. Twelve hours after ulcer induction, treatment was started, with a daily dose of each vehicle administered by oral gavage for three consecutive days. It was found that the wounds treated with Copaifera had a significantly smaller lesion area when compared to the group treated with corticosteroids, and the control in addition to a decrease in the acute inflammatory reaction and greater re-epithelialization. On the seventh day, the sores completely disappeared in the Copaifera-treated group. The animals in all groups showed complete wound closure on the 15th day. Levels of kidney and liver function tests did not reveal the presence of post-treatment damage.

In contrast, the study by Wagner et al. (2017) [14] demonstrated the effects of topical Copaiba oil extract and topical corticosteroid on healing of oral wounds in 96 Wistar rats. The authors suggest that topical administration of Copaifera oil did not accelerate the healing process of oral wounds. The authors recognize the study design as a limitation that may have resulted in the lack of significant results, as well as the chosen route of administration may also have contributed to non-significant results. An important point was that no adverse effects were observed after the administration of Copaiba, contrary to the use of Clobetasol, in another experimental group. It is important to point out that the concentration of the extract can be pointed out as a possible cause for the ineffectiveness of Copaiba oil in wound healing reported by other authors. Additionally, according to Dias da Silva et al. (2013) when systemic administration of EO's is performed, the anti-inflammatory effects of Copaifera seem to be potentiated [15].

Although the focus of this present integrative review is the use of essential oils in the oral cavity in experimental models, it is important to point out that their use on the skin has also shown excellent results. The study by Waibal et al. (2021) carried out with 42 healthy patients of both sexes, aged between 18 and 65 years, documented the effectiveness of Copaifera oil in silicone gel in reducing scar formation. Eligible patients had raised scars resulting from surgery, laser procedures, burns, and/or wounds whose scar age was not greater than 120 days. All patients in this study

had improvement in their scars. A visible scar reduction was observed with photographic evaluation in about 84 days. Eighty-nine percent of patients said they were satisfied or very satisfied with the result. The study showed significant improvement in the color, contour, distortion and texture of different types of scars using the Manchester Scar Scale.

Although there are studies that have investigated and proven the positive properties of using Copaifera oil for the management of oral and cutaneous lesions, its action on bone tissue is still little explored in the literature. The first study that addressed this issue was carried out by Dias da Silva et al. (2013) [15] with 28 Wistar rats that had their lower first molars extracted and divided into four groups, according to the treatment performed: (A) alveolus irrigation with Copaiba oil; (B) alveolus irrigation with saline solution; (C) daily gavage with Copaiba oil or (D) daily gavage with saline solution. The authors concluded that the topical and systemic administration of Copaiba oil can promote better results after oral surgical interventions.

In the construction of this present review, it was found that only one study that included analysis of Tea tree oil in the repair of oral lesions. However, it was developed in the context of oral candidiasis. In the study by Rasteiro et al. (2014) [17] twelve immunosuppressed rats with oral candidiasis received topical applications of Tea tree oil, which proved to be efficient in eradicating the *C. albicans* biofilm. Although the objective of the study by these authors was to analyze the inhibition of candida growth, an improvement in the superficial pattern of the lesion and tissue repair was also observed and, for this reason, it was included in this review.

EO's has shown to be promising agents in the management of healing, both in oral lesions and in skin lesions, and can be associated with methods that promote healing such as ozone therapy, photobiomodulation, among others. In the study by Mororó et al. (2020) [18] the effectiveness of using a Copaifera and Tea tree gel associated with ultrasound in skin lesions was documented. The composition of the oil in gel facilitated its application and contributed to the reduction of wound edge maceration, as well as to the control of wound edema.

In addition to the oils mentioned in this present review, several others seem to

contribute directly or indirectly to the healing of the oral mucosa due to their therapeutic properties. In addition to their low cost, these have the advantage of being manageable and can be used in association with other healing agents or even exclusively. Data from the study by Kaplan et al. (2020) ^[19] demonstrate that the use of Hypericum essential oils (St. John's wort) and Olive oil were efficient when their effects were compared to the gold standard mouthwash with chlorhexidine gluconate in reducing complications postoperative effects and improved healing without adverse effects after surgical removal of impacted third molars. Additionally, the study conducted by Alam et al. (2018) ^[20] analyzed different formulations of eucalyptus essential oil nanoemulsion regarding their wound healing potential. It was found that the wound healing potential of the optimized nanoemulsion was significant and even greater compared to pure eucalyptus essential oil. Histopathological examinations of mice treated with optimized nanoemulsion showed no signs of inflammatory cells, suggesting that the prepared nanoemulsion was safe and non-toxic for the animals.

Conclusion: This systematic review allowed observing the positive effects of using Copaifera and Tea tree essential oils in tissue repair in experimental studies. EO's represent an effective and low-cost therapeutic alternative for the oral wound repair. However, more scientific evidence is needed to expand its safe and effective use.

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