DOI: 10.53660/CLM-3775-23P32

Copaiba oil on dentistry: a scoping review

Óleo de copaíba na odontologia:uma revisão de escopo

Received: 15-06-2024 | Accepted: 19-07-2024 | Published: 23-07-2024

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ABSTRACT

Copaiba oil is a natural product commonly employed in traditional medicine due to qualities as anti-inflammatory and antimicrobial mainly. On dentistry, studies have focused on the use of copaiba in cavity varnishes, endodontic cements, bacterial biofilm control and even in the composition of local anesthetics. The aim of this study was to investigate on the use of copaiba oil within dental specialties. The search was conducted on databases using the primary keywords '*Copaifera'* and 'Dentistry' resulting in 687 studies. Was observed that *Copaifera multijuga* was the most prevalent species in the evaluated articles, endodontics was the most presente dental specialty in publications. Antimicrobial tests and biocompatibility tests was most prevalents. Based on the results of this study, despite the limited number of evaluated works, it can be concluded that over the years, copaiba has been increasingly used in dentistry, yielding promising results such as the development of new bioproducts that combine copaiba's pharmacological characteristics without compromising the necessary physical attributes for clinical use.

Keywords: Phytotheraphy; Copaifera; Biomaterials;Dental Materials.

RESUMO

O óleo de copaíba é um produto natural comumente empregado na medicina tradicional devido a suas qualidades como antiinflamatório e antimicrobiano. Na odontologia, os estudos têm se concentrado no uso da copaíba em vernizes cavitários, cimentos endodônticos, controle de biofilme bacteriano e até mesmo na composição de anestésicos locais. O objetivo deste estudo foi investigar a utilização do óleo de copaíba nas especialidades odontológicas. A busca foi realizada em bases de dados utilizando as palavras-chave primárias '*Copaifera*' e 'Odontologia' resultando em 687 estudos. Observou-se que a *Copaifera multijuga* foi a espécie mais prevalente nos artigos avaliados e Endodontia foi a especialidade odontológica mais presente nas publicações. Os testes antimicrobianos e os testes de biocompatibilidade foram os mais frequentes. Com base nos resultados deste estudo, apesar do número limitado de trabalhos avaliados, pode-se concluir que ao longo dos anos, a copaíba tem sido cada vez mais utilizada na odontologia, trazendo resultados promissores como o desenvolvimento de novos bioprodutos que combinem as características farmacológicas da copaíba sem comprometer os atributos físicos necessários para uso clínico.

Palavras-chave: Fitoterapia;*Copaifera*; Biomateriais;Materiais dentários.

INTRODUCTION

Biocompatibility has become a crucial concern in modern Dentistry, particularly when direct contact of the product with dental tissue is necessary. Copaiba oil is a phytotherapic product extracted from trees founds in South America, specially in Brazil. Possesses wound-healing, analgesic, anti-inflammatory, antibacterial (Cavalcante *et al.* 2021), biological, and physical properties that render this herbal remedy highly intriguing in the dental field (Silva *et al*.2019).

Oral bacteria are closely associated with diseases such as gingivitis, periodontal disease, dental caries, and endodontic infections affecting individuals of all age groups. The use of antimicrobials that eliminate bacteria or inhibit their excessive growth in oral infections is imperative. Dental materials, depending on their purpose, can act as antibacterials and also as a physical-chemical barrier, preventing potential reinfection, such as calcium hydroxide and zinc oxide-eugenol cements (Abrão *et al.* 2018).

On the other hand, eugenol, present in a variety of dental cements, is a material gradually being replaced due to cytotoxicity and interference in resin polymerization (Galazi *et al*.2015). In this context, copaiba oil is a potential substitute for eugenol, as it has been described as antimicrobial in primary endodontic infections and caries, without inducing cytotoxicity (Garrido *et al*.2010). Additionally, in a study involving patients with periodontitis, the use of copaiba oil significantly reduced inflammatory profiles, limiting alveolar bone loss and increasing trabecular thickness and bone-tissue ratio compared to an untreated periodontitis group (Dos Santos *et al*.2022).

Concerning the observed physical properties of copaiba oil, such as tensile strength of a copaiba resin oil-based dental cement compared to RelyX Temp NE provisional cement (3M, Sumaré-SP, Brazil), crowns cemented with the test cement exhibited better retention (Lima *et al*.2023). When comparing working time, flow, film thickness, dimensional stability, radiopacity/disintegration of copaiba-endodontic cement to Sealer 26 (Dentisply, São Paulo – SP, Brazil), Endfill (Dentisply, São Paulo – SP, Brazil), and AH Plus (Dentisply, São Paulo – SP, Brazil), it was concluded that copaiba cement demonstrated satisfactory results and physical properties, in accordance with ADA 57, regulating characteristics of endodontic cements (Garrido *et al*.2015).

Thus, the objective of this study was to assess the use of copaiba oil in different dental specialties through a scoping review without restrictions on the publication year.

MATERIALS AND METHODS

The primary English/Portuguese keywords, consulted in the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCs) vocabularies, were Copaifera and Dentistry. After reviewing 10% of the articles, the following secondary keywords, listed in Table 1, were employed.

Table 1- Search strategy

Subject	Terms
Copaifera	*"Copaifera"* OR "Amazonian copaiba oils" OR "oil of *Copaifera multijuga* Hayne", OR *Copaifera multijuga*" OR "*Copaifera* oleoresin" OR "*Copaifera Langsdorffii* Oil Resin"
Dentistry	"teeth" OR " tooth" OR "dentin" OR "cement" OR "pulpotomy" OR "cytotoxicity" OR "dental pulp"OR "antimicrobial" OR "gingivitis"OR "tong"
Type of study	"double blind" OR "single blind" OR "randomized"OR "placebo" OR "Randomized controlled trial" OR "controlled clinical trial" OR "trial" OR "randomly" OR "group"

Were included in this review works published in English, Portuguese, and Spanish that examined the use of copaiba oil-resin in dentistry. In this context, the intended outcomes for this scoping review were the effects of copaiba oil-resin in its natural state, diluted, or in formulations applied to dental tissues and oral mucosa, either in vitro or clinically, in animals or humans.

The following types of articles were excluded: case reports, case series, editorials, ecological studies, reviews, unpublished studies, and studies that did not involve testing copaiba on oral tissues.

Initially, articles were selected based on the reading of the title and abstract, and those meeting eligibility criteria were chosen through consensus between two reviewers (C.C.L. and M.H.R.B.) for the potential inclusion of articles. Among the selected articles, a full-text reading was conducted for inclusion or exclusion in the review according to the criteria of interest. Discrepancies at this stage were resolved through consensus with a third reviewer (D.M.S.). Article categorization and removal of duplicates were performed using the Rayyan platform.

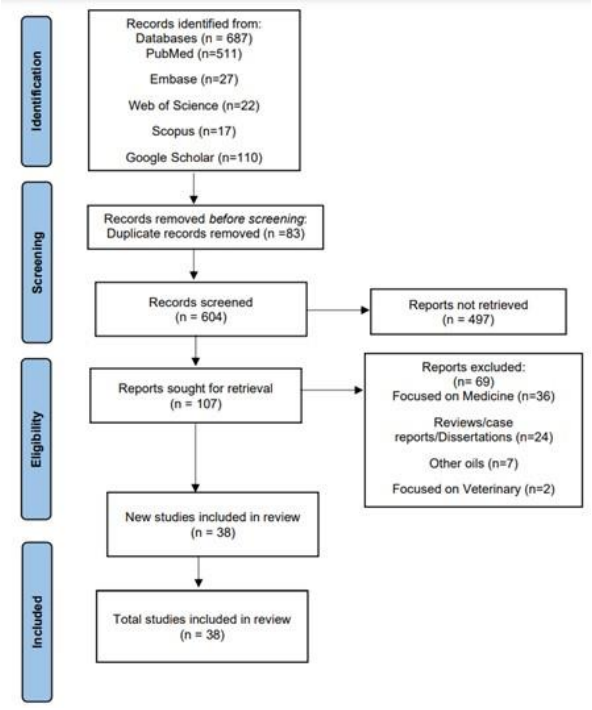
The included studies had their data summarized by two evaluators, utilizing a tabulation approach with the following information: author, year of publication, study type, *Copaifera* species, dental specialty, form of exposure used (copaiba oil-resin in its natural state/essential oil included or not in experimental formulations), objective (antibiosis, biocompatibility, tensile strength, and anti-inflammatory effects), study methodology, and results.

Using the Cochrane Collaboration tool, three reviewers (C.C.L., M.H.R.B., and D.M.S.) independently assessed each study for bias risk in five applicable domains: patient and personnel blinding, outcome concealment, incomplete data and results, selective reporting, and sources of exclusion. The overall risk of bias for each study was considered high if the bias risk was high in any domain, inconclusive if bias was unclear in all domains, and low if the bias risk was low in all domains.

RESULTS

In accordance with the criteria defined for this review, 687 articles related to the primary and secondary keywords were founded in the databases from January and Febuary 2024 (Figure 1).

Figure 1- Flowchart of study selection



Among these, 511 were found in PubMed, 27 in Embase, 22 in Web of Science, 17 in Scopus, and 110 in Google Scholar. After removing duplicates, the title and abstract content criteria were applied to 604 results, with 83 being excluded for deviating from the theme. Six hundred and four works had their full text read, and according to the eligibility criteria, 497 were excluded, of wicht 69 for the following reasons: studies outside the theme, other types of oil, studies focused on the medical or veterinary field, reviews or case reports, and dissertations. Finally, 38 were included for review published between 2008 and 2023.

Basead on publications, its possible to observe that copaiba oil resin show a large inhibition of gram positive and gram negative bacterial growth presented on oral diseases (Table 2) and can promoted significant reduction of *Candida* adhesion.

Table 2- Resume of tests showing bacteria growth inhibition with copaiba.

Specie	Bacteria	Concentration
Copaifera multijuga[1]	*S. mutans,S. sanguinis*	100%
Copaifera officinalis[2]	*S. mutans*	10%
Copaifera reticulata[3]	*Porphyromonas gingivalis*	3,43%
Copaifera oblongifolia[4]	*E. faecalis, S. salivarius, S. sanguinis, S.mutans, S. mitis, S. sobrinus, L. casei, A. A., P. gingivalis, P .intermedia, P. nigrescens, P. buccae, F.nucleatum,B. fragilis, B. thetaiotaomicron, A. naeslundii, A. viscosus and P. micros*	25- 200 μg/mL
Copaifera duckei Dwyer[5]	*Actinomyces naeslundii, Lactobacillus casei*	< 100 μg mL^{-1}

References:1 Vasconcelos *et al.* (2008);2 Pieri et al.(2012);3 Perfecto e Luna (2014);4 da S Moraes *et al. (2016); 5* Abrão *et al.(2018).*

The literature suggested that the hydrocarbon sesquiterpenes present in the copaiba oils are responsible for the anti-inflammatory action reported on folk medicine (Veiga *et al*.2001). With methods varying according to the area of application in oral tissues, clinical, *in vivo* and *in vitro* studies were found (Table 3) evaluating the possibility of reducing the inflammatory process on oral tissues with copaiba apply: After pulpotomy (Lima *et al*. 2011), alveolar wound healing after tooth extraction (Dias-da-Silva *et al.* 2013), incisions in tongue tissue, and induced periodontitis (Teixeira *et al.* 2017; Alvarenga *et al.* 2020). Except in study of Wagner *et al.* 2017, copaiba provided a considerable reduction in the effects of inflammation in the lesions studied.

Table 3- Resume of studies evaluating anti-inflammatory properties applicable to Dentistry included in the review.

Specie	Objetive	Result
Copaifera langsdorffii[1]	Inflammatory effect of copaiba oleoresin after pulpotomy in deciduous teeth.	Less severity in the inflammatory process.
Copaifera reticulata[2]	To evaluate the anti-inflammatory and healing effects of copaiba on tongue lesions in rats.	A smaller wound area was detected, a reduction in acute symptoms at inflammatory reaction and greater re-epithelialization
Copaifera reticulata[3]	To evaluate the effect of systematic administration of copaiba oleoresin in rats with induced periodontitis.	Considerable reduced the inflammatory

References:1 Lima *et al.* (2011);2 Alvarenga et al.(2017);3 Dos Santos *et al.* (2022).

Were found nine articles evaluating, between another aspects, the biocompatibility of copaiba in dental materials (Table 4): Copaiba as vehicles presented satisfactory tissue reaction in the connective tissue of rats (Garcia *et al*. 2011), satisfactory cytocompatibility (Silva *et al.* 2016;Reiznautt *et al*.2021), not affect bone formation (Silva *et al.*2015), and can be suggested as a pulpotomy agent for primary teeth (Musale e Soni 2016; Couto *et al.*2020). Furthermore, an emulsion containg copaiba showed decreased of antiproteolytic activity of metalloproteinases in human tooth (Araújo *et al.* 2021), a great propriety on a biomodifier in dental tissue to improve the interface bond betwwen adhesive systems and dentin.

Table 4-Resume of studies with copaiba citotoxicity tests.

Specie	Cell/tissue	Result
Copaifera multijuga[1]	Osteoblasts Osteo-1	Not show a decrease in cell viability.
Copaifera multijuga s[2]	V79 fibroblasts	Intermediate level of cell viability.
Copaifera reticulata[3]	Human dental pulp cells	Impruve differentiation, mineralization and migration
Copaifera spp.[4]	Mouse fibroblasts L929	Cell viability above 80 %

References:1 Garrido *et al*. (2015);2 Silva *et al*.(2016);3 Couto et al. (2020);4 Reiznautt, *et al. (2017).*

An emulsion containg copaiba showed positive effecton dentin bond marginal adaptation and some studies demonstrate that is possible incorporate copaiba on dental

when avalied working time, fluidity, film thickness, dimensional stability, radiopacity, solubity and tensile strength (Table 5).

Table 5 - Description of the characteristics of the some studies evaluating physical properties of dental products developed with copaiba.

Objetive	Results
Working time, fluidity, film thickness, dimensional stability, radiopacity/disintegration of sealer based on Copaifera multijuga oil-resin	Physical properties in accordance with American Dental Association.
Dimensional alterations and the solubility of sealer based on Copaifera multijuga oil-resin	Showed low solubity in simulated tissue fluid,
Effect of prior application of copaiba oil emulsions as a dentin cleaning substance on microleakage and microtensile adhesive strength.	Positive effect on strength of dentin bond and marginal adaptation.
Test the fracture resistance of tooth fragments immersed in distilled water, an emulsion based on Copaíba oil.	Dentin treated with copaiba emulsion showed a higher modulus of elasticity

Most of the studies, sixteen in total, were laboratory tests evaluating the antimicrobial capacity of copaiba against oral pathogenes, especially endodontic cements (Figure 2). According to the results (Figure 3), the species most present in the studies was the *Copaifera multijuga*.

Figure 2-Number of articles X type of tests present in the review articles.

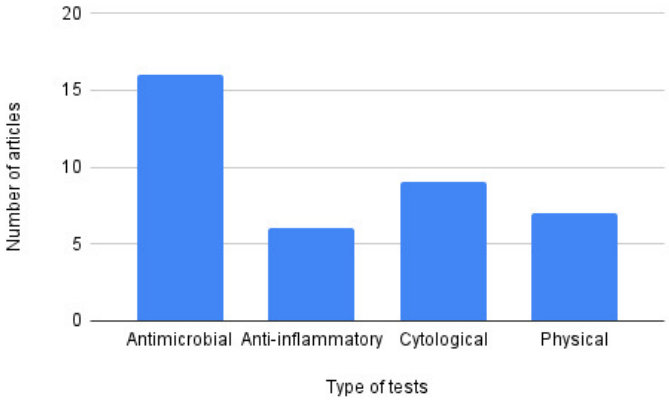
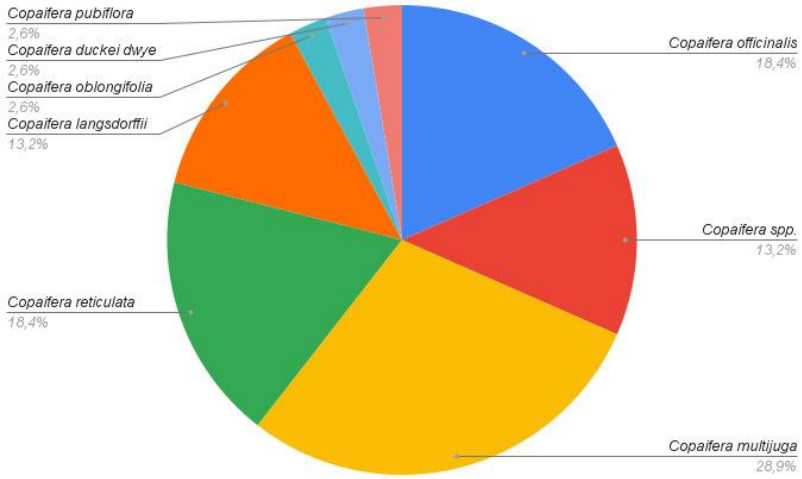
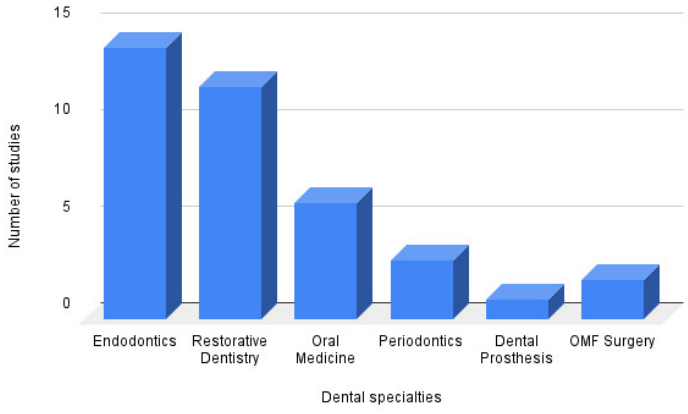


Figure 3-Percentage of *Copaifera* species found among the studies used in the review.



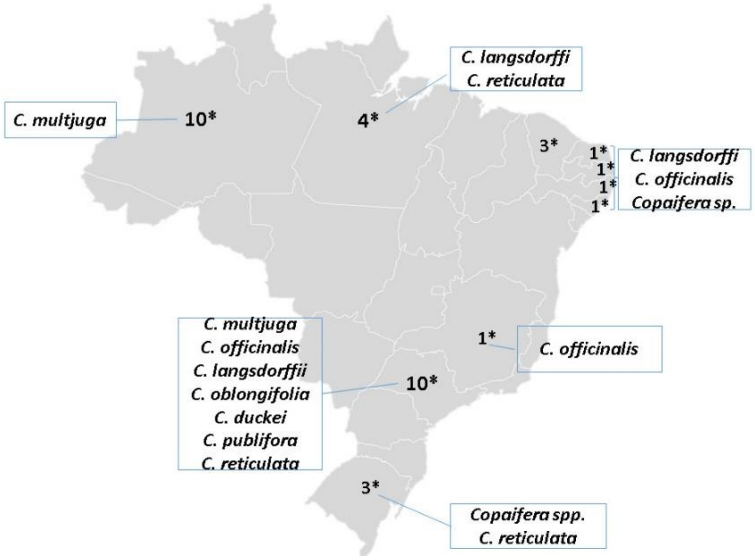
Of the dental specialties present in the articles found, twelve evaluated the use of copaíba in Endodontics, eight in Restorative dentistry/cariology, five in parameters studied by Oral medicine, three evaluated the effects of copaíba in Periodontics, two in Oral and maxillofacial surgery and only one was focused on the area of Dental prosthesis (Figure 4).

Figure 4- Number of studies x dental specialties included in the research.



With the exception of one study carried out in India,one in Perú and another on Mexico, all others were carried out in Brazil: ten in the state of Amazonas, ten in São Paulo, four in Pará, three in Ceará, three in Rio Grande do Sul and in Alagoas, Rio Grande do Norte, Paraíba, Pernambuco and Minas Gerais, only one article included (Figure 5).

Figure 5- Geographic distribution of the copaiba species studied, and number of articles written by Brazilian state (*number of articles published by state).



DISCUSSION

The present review synthesized the evidence on the possibility of successful use of copaiba oleoresin in dentistry due to its antimicrobial and anti-inflammatory effects, anti-proteolytics, due to their low cytotoxicity and dimensional stability necessary for a dental material, according to the purpose studied.

Endodontics was the dental area that had the highest frequency in the articles found, mainly with antimicrobial tests and evaluation of physicochemical characteristics of formulations containing copaiba. Three articles tested experimental cements with copaiba and the same components, and Garrido and collaborators (Garrido *et al*.2010; Garrido *et al*.2015) have more than one publication with tests to the development of Biosealer, an endodontic cement containing copaiba in its composition, already patented.

As for the Brazilian location with the highest number of articles present in the review, São Paulo and Amazonas has the highest number of publications, of with used *Copaifera multijuga* from trees native to the state. Therefore, it can be inferred that this result is linked to the abundance of that species in the region and the logistical ease of obtaining this raw material.

However, according to the data collected, due to the multiplicity of methodologies in the articles, regardless of the dental specialty, it was not possible to reach a consensus

regarding the species of *Copaifera* most compatible with the tissues and oral microbiota, what concentration of oil it has or not. Some type of selectivity towards oral pathogens and what is the best physical presentation of the dental product that preserves the active ingredients present in the composition of the natural oil.

Copaiba oleoresin is a potential antimicrobial against bacteria involved in primary endodontic infections and dental caries (Valadas *et al.* 2019;Moraes *et al*.2020;Valadas *et al*.2021).In a study Vasconcelos et al. (2008) seeking to obtain the Minimum Inhibitory Concentration (MIC) of *Copaifera multijuga* Hayne oleoresin against *Streptococcus mutans* and *S. sanguinis* in a cement containing zinc oxide, calcium hydroxide and copaiba using as control the three components alone, the authors observed that although all groups tested showed antibacterial activity, which leads to the belief that the developed cement has a promising use in dentistry, the oil resin alone showed the best results.

Pieri et al. 2012 evaluated the MIC of *Copaifera officinalis* oleoresin against *S. mutans*, and observed that the 0,12% chlorhexidine solution was effective up to 6,25 μL/mL in the broth, while the oil of copaíba showed inhibition of bacterial growth at all concentrations tested up to 0,78 μL/mL of 10% copaíba oil solution in the broth, meaning that copaíba oil has bacteriostatic activity against *S. mutans* at low concentrations, which can be an option for a phytotherapeutic agent to be used against cariogenic bacteria in the prevention of caries disease.

About use on cements, the results of Silva *et al.*2016 showed that when the cytotoxicity and genotoxicity of an endodontic cement containing copaiba extract was tested using a cement containing castor oil, AHPlus, EndoREZ and RealSeal SE as controls in V79 hamsters, the copaiba-based cement showed an intermediate level of cell viability, comparable to commercial cements, however, it was more cytotoxic than castor oil, and did not have a significant genotoxic effect, which shows that copaiba is not totally inert when in contact with living cells.

However, Reiznautt *et al.* (2016) concluded in their study that endodontic cement containing copaiba had cytocompatibility, antimicrobial effects and satisfactory physicochemical properties when compared to RealSeal endodontic cement.

Seeking to evaluate the behavior of the copaíba *Copaifera langsdorffii* in tooth pulps after pulpotomy, comparing with propolis extract, fibrin sponge and an iodoform

paste, Lima et al.(2011) observed that there was a predominance of neutrophils in the inflammatory process in samples from all the groups, with milder intensity in the copaíba group, which was also the only group that did not have an increase in the intensity of the necrosis regions and where there was the formation of a barrier of mineralized tissue in the exposed pulp regions protected by the oleoresin.

With a similar objective, Musale e Soni (2016), in a clinical study, observed that *Copaifera langsdorffii* had the highest frequency of pathological radiolucency in 12 months. Radiographic success at 12 months was lower when compared with formocresol and MTA, respectively, meaning that *Copaifera langsdorffii* oil resin can be suggested as a pulpotomy agent for primary teeth for up to a year.

Couto *et al*.2020 using mesenchymal cells derived from the human pulp of deciduous teeth, observed that the combination of copaiba of the genus *Copaifera reticulata Ducke* with calcium hydroxide and MTA improved cellular activities related to pulp regeneration, including a protective effect against the cytotoxicity of calcium hydroxide, further confirming a tissue repair effect of copaiba.

Some studies have demonstrated that copaiba has limitations in its use in some types of formulations, such as Pereira et al.(2010) when evaluated the anti-plaque and antigingivitis effect of *Copaifera sp*. in a split-mouth study, observing that the gel containing 10% copaiba did not prevent the formation of biofilm and the development of gingivitis, as did the use of 5% copaiba in a toothpaste formulation, as demonstrated by Dos Santos *et al.* (2021).

But, Perfecto e Luna (2014) compared the antimicrobial activity of copaiba oleoresin against *Porphyromonas gingivalis* with 0.12% chlorhexidine, and in this work, copaiba showed effective inhibition of the growth of *P. gingivalis*, surpassing the action of chlorhexidine at 0.12%.

Simões et al. (2016)evaluated *in vitro* the antimicrobial activity of a copaiba gel against *Streptococcus sp*. comparing with 1% chlorhexidine gel, but due to factors related to methodology, as may have happened in the study with the 10% gel by Pereira et al. (2010), such as the difficulty in diffusing the gel in the culture medium, for example, antibacterial activity was obtained only within a 24-hour period, with microorganisms being resistant to the gel in the period following and after this interval. As well as, with

regard to the inhibition halos of chlorhexidine, which were larger, which does not mean a greater antibacterial activity than the copaiba gel, which when tested alone on oral bacteria, presented a favorable perspective for future use in the control of biofilm.

Gomes *et al.* (2023) after previous analyses realized by Bari *et al.* 2016 and Bandeira *et al.*2020, tested the fracture resistance of tooth fragments immersed in distilled water, an emulsion based on Copaíba de Copaifera multijuga oil and 2% chlorhexidine, where the said product provided the dentin treated with the copaiba emulsion with a higher modulus of elasticity when compared to chlorhexidine.

Mainly due to the low cost and fewer side effects, the comparison between experimental formulations with herbal extracts and commercial products is common in the pharmaceutical area, as well as in dentistry. However, the low number of studies aimed at the development of new dental bioproducts demonstrates the need for incentives in this regard, both in the scientific area, for the protection of the genetic heritage of Brazilian fauna, in the aspect of developing national patents, and for incorporation into popular medicine of additional qualities that copaiba oleoresin can offer.

CONCLUSIONS

The results of this systematic review suggest that copaiba oleoresin from different species and subspecies has the potential to be satisfactorily included in dental applications due to its biological and physical properties, comparable to existing commercial products. However, additional studies are needeeds so that the clinical feasibility of incorporating these phytopharmaceuticals becomes completely safe.

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