



## Minireview about Medicinal Copaiba Oil in the Treatment of Skin Diseases

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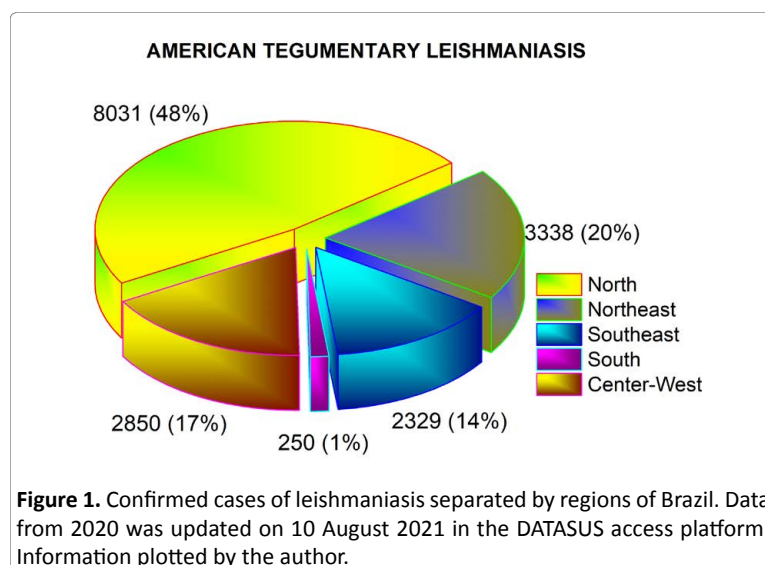
### Abstract

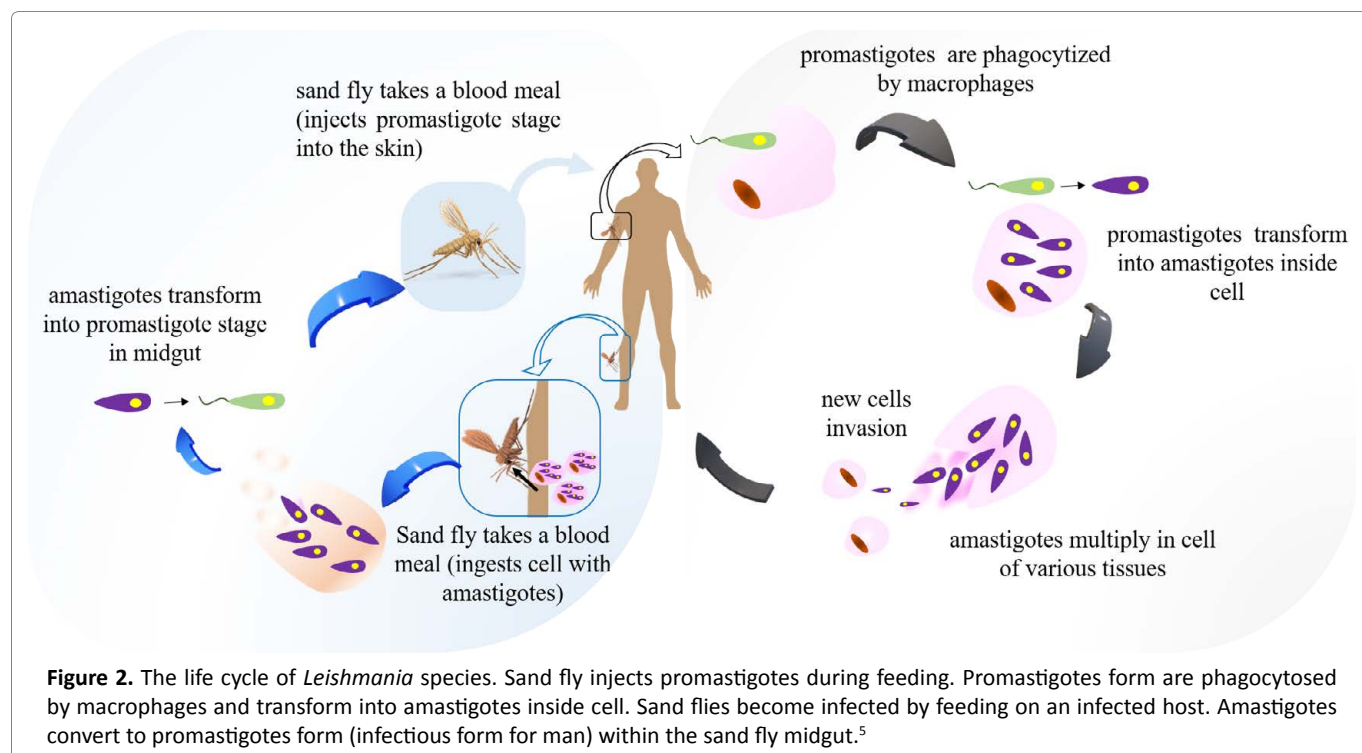
The therapeutic benefits of copaiba oil-resin have encouraged its use in developing dermatological emulsions. Here, the anti-inflammatory, healing, antimicrobial, analgesic, and permeation-promoting properties of this medicinal oil are shown by reviewing articles from 2005 to 2021. Their properties encourage research to develop an herbal medicinal effective in treating skin diseases and cutaneous leishmaniasis.

### Introduction

The Brazilian scenario of infectious and parasitic diseases faced a significant increase from 2018, the so-called epidemiological transition. The battle between humanity and pandemics is a significant challenge for public health, especially for developing countries such as Brazil.<sup>1</sup> As a side effect of the ecological mismatch, Brazil faces the proliferation of epidemic diseases, such as leishmaniasis. Figure 1 shows the distribution of confirmed tegumentary leishmaniasis cases in 2020, emphasizing the north Brazilian region. In recent years, the frequency of this parasitosis has raised medical and scientific concerns, requiring the search for effective and accessible strategies for the population served by the Unified Health System (SUS).

The higher incidence in the north Brazilian region is linked to the lack of basic sanitation, scarce health care, the precarious economic





situation, disorderly urban occupation, excessive contact with animals that serve as reservoirs of the disease, and deforestation and mining activities.<sup>2,3</sup>

Leishmaniasis is transmitted by biting infected females (vectors, popularly known as the sand fly) of the Phlebotominae subfamily (Figure 2). The amastigotes (ingested by the fly during blood repast) convert to promastigotes form (flagellates) in the sand fly. Subsequently, the promastigotes form is inoculated into mammals' skin during biting.<sup>4</sup>

In intravenous or intramuscular doses, leishmaniasis treatment has been performed with N-methyl glucamine antimoniate and pentavalent antimonials. In addition, Amphotericin B deoxycholate or liposomal amphotericin B by intravenous infusion is also reported, with dosages established by the regulatory agencies.<sup>3</sup> However, these therapeutic strategies have disadvantages due to dose-dependent acute adverse effects, which require hospitalization for drug administration, with the possibility of emergency tracheostomy.<sup>6</sup>

Dermatological treatments can be achieved using herbal formulations therapeutically based on copaiba oil-resin (COR).<sup>7-10</sup> COR is a medicinal bioactive approved by the Food and Drug Administration (FDA)<sup>11,12</sup> and commercialized in Brazil to combat more than 50 diseases, being included as a promisor agent against Sars-CoV-2 by molecular docking studies.<sup>13</sup> This mini-review aims to bring to the scientific community the potential of COR for several skin diseases treatment, especially cutaneous leishmaniasis. This oil-resin has shown potential in leishmaniasis treatment,

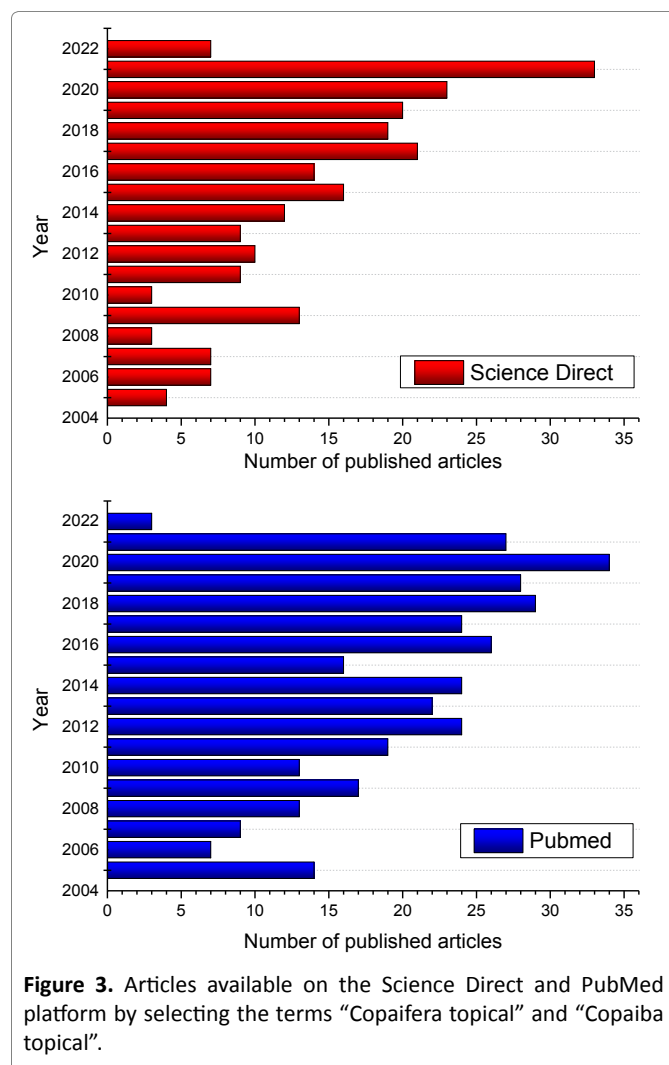
with IC<sub>50</sub> values of 7.88 µg.mL<sup>-1</sup> for promastigotes and 0.52 µg.mL<sup>-1</sup> for amastigotes; data statistically equivalent (p>0.05) to Pentamidine and Amphotericin B.<sup>14</sup>

The main articles related to the benefits of using copaiba oil for dermatological purposes (dating from 2005 to 2021) were selected in this mini review. While COR has excellent potential in treating skin diseases, a small percentage of these articles address topical formulations with resin oil to treat cutaneous leishmaniasis.

### Dermatological Therapeutic Effects of Copaiba Oil-resin

The interest in copaiba oil has increased significantly in recent years. For example, between 2005 and 2022, the Science Direct and Pubmed platforms provided 579 available searches with "*copaifera topical*" and "*copaiba topical*" as the selection, with more than 50% published between the years 2017 and 2022 (Figure 3). This fact demonstrates the growing recognition of the therapeutic effects of this oil-resin.

The benefits of this medicinal oil can be attributed to its composition. Copaiba oil is rich in sesquiterpenes (volatile fraction) and diterpenes (resinous fraction).<sup>15</sup> The antiinflammatory activity was attributed to hydrocarbons and sesquiterpenes (especially β-bisabolene and β-caryophyllene).<sup>7</sup> Carvalho et al., (2005) evaluated the antiinflammatory and analgesic activity of *Copaifera reticulata* Ducke in topical administration (*Rattus norvegicus*). Besides, the authors evaluated granuloma tests related to the dermatitis inflammatory process. Daily



doses of copaiba oil were from 517 mg to 1802 mg.kg<sup>-1</sup> animal, being 1802 mg.kg<sup>-1</sup> dose most effective in inhibiting edema and granuloma tissue.<sup>7</sup>

Estevão et al., (2013) evaluated the effects of copaiba oil ointment (*Copaifera langsdorffii* at 10 % w/w) on rat skin lesions. The authors found a less necrotic area and more granulation tissue, with bulky fibroblasts and collagen fibers arranged using copaiba ointment.<sup>16</sup> Furthermore, De Oliveira et al., (2010) reported the advantages of using copaiba oil in dermatological treatments. The authors showed that the oil-resin acts as a skin penetration enhancer in drug combination therapy.<sup>17</sup> This property is probably due to the emollient character of the formulation.<sup>18</sup> Dermatology also highlights the use of copaiba oil in Acne Vulgaris and skin wound treatment, as reported in the literature.<sup>19, 20</sup>

Maragon et al., (2017) developed antimicrobial formulations composed of copaiba oils acquired from different regions, being OCA abbreviation regarding resin oil purchased from São Paulo, OCB from Belém, and OCC from Pará. The formulation matrix was chitosan/gelatin

gels derived from pig skin in a 2:1 w/w ratio (QG matrix). Evaluations were performed against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and Vero cell line cytotoxicity studies. The authors noted minimum inhibitory concentration (MIC) values for the QG matrix (without drug) between 31 and 62 µg.mL<sup>-1</sup> for the three pathogens evaluated. The antimicrobial activities of OCA, OCB, and OCC copaiba oils (unformulated oil) showed the highest activity against *S. aureus*, with MICs of 2.0x10<sup>3</sup> µg.mL<sup>-1</sup>, 500 µg mL<sup>-1</sup>, and 62.5 µg.mL<sup>-1</sup>, respectively. Dealing with the QG emulsions containing copaiba oil, the authors reported improved results only for the QG-OCC system. A synergistic effect was observed for this formulation, reducing the bactericidal concentration compared to the individual components. Cytotoxicity evaluations of the individual components (OCA, OCB, and OCC) showed that only OCC showed no cytotoxic effect on Vero cells. However, after formulation, all systems were shown to be pharmacologically safe.<sup>21</sup>

Becker et al., (2019) studied the antinociceptive and antiinflammatory properties of a formulation of the copaiba oil (3 %) to treat sunburn-related inflammatory pain. The developed formulation was characterized by temporal stability, organoleptic characteristics, pH, spreadability, and rheological profiles. Furthermore, the authors used a UVB radiation-induced skin burn model (0.75 J.cm<sup>-2</sup>) in rats and performed daily administration of the cream formulation. Overall, the developed copaiba gel proved to be stable during the analyzed period and allowed antinociceptive and anti-inflammatory effects in animals exposed to UVB radiation. These benefits were linked to the presence of β-caryophyllene and other sesquiterpenes identified by gas chromatography. Therefore, the authors considered the use of copaiba oleoresin as a promising strategy.<sup>22</sup>

Nigro et al., (2020) evaluated the use of resin oil as a potential replacement for Coenzyme Q10 (CQ10). CQ10 is a beneficial substance in wound treatment due to its antioxidant and healing properties. However, when formulated, CQ10 offers low skin permeation capacity, in addition to its susceptibility to photodegradation. Its permeation is desired to protect keratinocytes from oxidative damage and favor fibroblast and collagen proliferation. The authors noted improvements in cell viability when using Q10 and copaiba oil-resin mixed formulation. Furthermore, the combination therapy showed benefits dependent on the droplet size of the emulsion; studies evidenced when comparing preparation methods involving manual and ultrasonic agitation.<sup>23</sup>

When it comes to wounds, some types present difficulties in healing and require new adjuvant therapies to be combined with conventional clinical treatments. In this process, micro-needling and low-frequency waves

can increase the healing speed of deep wounds. Studies have already reported the advantages of the cutaneous administration of copaiba oil by micro-needling on collagen and fibroblast production.<sup>24</sup> In the same way, the use of ultrasound associated with conventional therapy showed benefits. Patients with wounds followed up by the hospital in Ceará state, Brazil, were treated with 10 sessions of ultrasonic therapy associated with the gel with copaiba and tea tree oil. The authors found a more than 50% reduction in the initial lesion size by the 10th session. Some patients showed complete healing by the 10th session (2 patients of 14 evaluated).<sup>25</sup>

In patients with leishmaniasis, the immune status must be considered when choosing the therapeutic approach. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine produced by macrophages that is important in defense of the host against infection by *Leishmania* species. However, the treatment of several diseases, such as rheumatoid arthritis and psoriasis, involves anti-TNF- $\alpha$  therapy. Consequently, these patients are usually afflicted with opportunistic infections, such as leishmaniasis and tuberculosis. Cases of cutaneous leishmaniasis in patients taking TNF- $\alpha$  are poorly described in the literature.<sup>26</sup> The use of copaiba oil (*Copaifera* sp.) has also been suggested as alternative medicine in treating rheumatoid arthritis, with doses that are still under investigation in the scientific field. The main component of the oil-resin that shows anti-inflammatory activity is  $\beta$ -caryophyllene.<sup>27</sup> There are indications that copaiba oil (100  $\mu\text{g}\cdot\text{mL}^{-1}$ ) also acts with mechanisms that inhibit TNF- $\alpha$ ; however, this behavior is still being investigated.<sup>28</sup>

### Antileishmanial Activity of the Copaiba Oil-resin

Although copaiba oil exhibits skin healing activities, its use as a leishmanicidal has been little explored. In Brazil, the works published by Santos et al., (2008) are considered a reference for making a broad sweep of copaiba oil species found in the Brazilian Amazon. The authors carried out important *in vitro* studies considering the antiprotozoal activity of the *Copaifera multijuga*, *Copaifera officinalis*, *Copaifera reticulata* Ducke, *Copaifera lucens*, *Copaifera langsdorfii*, *Copaifera paupera*, *Copaifera martii* and *Copaifera cearenses* against *Leishmania amazonensis*. The data showed different activity levels against the promastigote form of *Leishmania amazonensis*, with  $\text{IC}_{50}$  ranging from 5.0 to 22.0  $\text{g}\cdot\text{mL}^{-1}$ . The biological activities were attributed to the group of sesquiterpenes (especially  $\beta$ -caryophyllene,  $\alpha$ -copaene, zingiberene,  $\beta$ -bisabolene, and bergamotene) and diterpenes (mainly hardwichiic, kovalenic, kaurenoic, polyallic, and copalic) existing in different amounts in the copaiba species. The *Copaifera reticulata* Ducke showed more significant activity than the others, with  $\text{IC}_{50}$  of 5.0  $\mu\text{g}\cdot\text{mL}^{-1}$  for the promastigote form and 15.0  $\mu\text{g}\cdot\text{mL}^{-1}$  for the amastigote form of *Leishmania*

*amazonensis*, after 72 h of incubation. Similarly, *Copaifera reticulata* Ducke showed marked activity against the amastigote form, with  $\text{IC}_{50}$  of 20.0  $\mu\text{g}\cdot\text{mL}^{-1}$ . The more significant activity of *Copaifera reticulata* Ducke than the others was attributed to the more significant presence of the component  $\beta$ -caryophyllene.<sup>29</sup> The mechanism of action of  $\beta$ -caryophyllene is not well understood. However, leishmanicidal drugs target the glucose transport system and *Leishmania*-specific enzyme systems.<sup>14</sup>

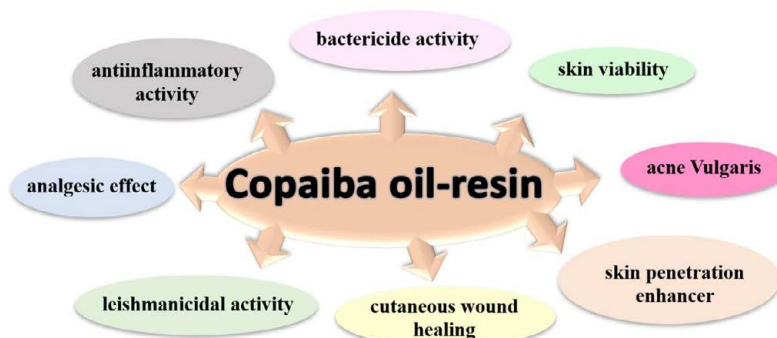
Dhorm Pimentel de Moraes et al., (2018) developed nanoemulsions of copaiba and andiroba oils for testing *L. infantum* and *L. amazonensis*. The nanoemulsions were composed of water (10 mL), Tween 80 (0.4 g), Span-80 (0.4 g), and oil phase (1 g) obtaining NanoCopa (with copaiba oil) and NanoAndi (with andiroba) formulations. The systems showed no considerable coalescence effects over 90 days and maintained their sizes between 76 and 92 nm (polydispersity values near 0.15). The *in vitro* and *in vivo* results obtained by the authors were satisfactory. The promastigote form of both *Leishmania* species proved to be sensitive to NanoCopa and NanoAndi. Morphological analyses of the protozoa after nanoemulsions treatment induced an oval cell shape and retracted flagella. In addition, the authors found a reduction in the infection levels caused by *L. infantum* and *L. amazonensis* in macrophage cultures. The use of copaiba nanoemulsions proved beneficial when considering *L. amazonensis*-induced lesion size, parasite load, and histopathology profile in BALB/c mice. Similarly, the treatment of *L. infantum* infected animals reduced the parasite load in the spleen and liver and improved the histopathological profile.<sup>30</sup>

### Stimulant-responsive Formulations for the Treatment of Cutaneous Leishmaniasis

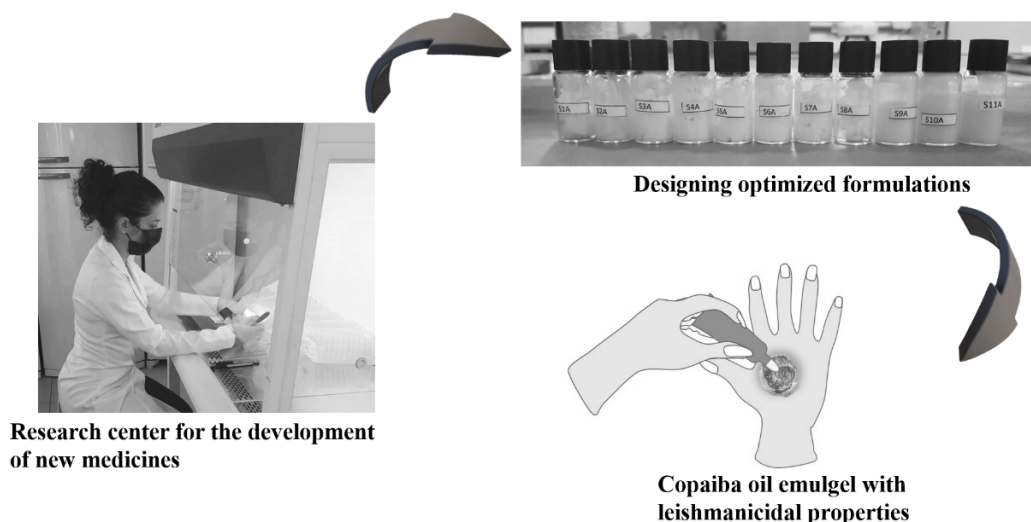
The union of research groups at the State University of Maringá, Paraná State, Brazil, develops optimized formulations containing high copaiba oil content. Extensive studies are conducted to evaluate the maximum content of copaiba oil that can be incorporated into topical formulations while ensuring good mechanical and rheological properties. Although the benefits of the bioactive are known, little research has been done to generate a dermatological gel with high performance before and after administration. The work proposed by the University of Maringá certainly has high market potential.<sup>10,31,32</sup> Figure 4 reports all the benefits of copaiba oil in dermatological treatments. Observations indeed resulted in the selection of the therapeutic oil in many Brazilian kinds of research.

Campanholi et al., (2021) sought an optimized thermoresponsive formulation containing high copaiba oil-resin. The authors proposed developing a dermatological gel to treat ulcerated skin or skin affected by cutaneous leishmaniasis. The evaluation of the stimulus-responsive properties took into account the range of viscosity values





**Figure 4.** Activities reported in scientific articles for copaiba oil-resin.



**Figure 5.** Image donated by Katieli S. S. Campanholi (photo) Ph.D. researcher, reporting on the cycle of new drug development performed at the State University of Maringá, Brazil.

before and after the end of the gelling process. The authors worked with concentrations of copaiba oil ranging from 15-25 % w/w, Pluronic F127 from 18-22 % w/w, and bioadhesive polymer carbopol, from 0.2 to 0.3 % w/w. The mechanical and rheological characteristics showed losses when a high oil concentration was incorporated. At the upper planning limit for oil and Pluronic, the system showed high consistency and impaired stimulus-responsive properties. The best properties were seen in the systems with the lowest loadings of Pluronic oil. Thus, the authors suggested that the lower limit of the components is promising in further design and optimization studies.<sup>10</sup> Figure 5 shows a photograph donated by the authors that shows the extensive study to improve the formulation with copaiba oil.

## Conclusion

The anti-inflammatory, leishmanicidal, healing, antimicrobial, analgesic, and permeation-promoting properties of copaiba stimulate studies seeking the development of high-performance drugs to treat cutaneous leishmaniasis.

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