

# Meta-analysis on Copaiba Oil: Its Functions in Metabolism and Its Properties as an Anti-inflammatory Agent

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## Abstract

Many medicinal plants are sought as alternative therapies for various conditions, as opposed to synthetic alternatives. The Brazilian Amazon provides a plethora of plants with various therapeutic and medicinal properties. One of them is copaiba oil, a natural product of the biodiversity of the Amazon. The anti-inflammatory and antimicrobial properties of copaiba oil have been drawing the attention of the scientific community as a great alternative in the treatment of illnesses associated with inflammatory and infectious processes. The purpose of the present study is to evaluate and analyze the latest publications on the use of copaiba oil in the PubMed/Medline database from 2014 to 2017. Forty-two articles were collected, verifying anti-inflammatory activity, antimicrobial activity, healing, and antitumor activity. The results found on researches with copaiba oil according to publication dates were 11.9% in 2014, 38.1% in 2015, 16.7% in 2016, and 33.3% in 2017. In the analyzed studies, the proposed administration of copaiba oil was 50% topical, 28.6% oral, 9.5% enteral, 4.8% subcutaneous, and 7.1% others. In the objectives of the present study in relation to the administration of copaiba oil, the result was 31% antimicrobial, 28.6% anti-inflammatory, 9.5% antitumor, 9.5% healing, and 21% others. Regarding the types of research, we have found 50% in vitro, 40.4% in vivo animals, 2.4% in vivo human, 2.4% review and 4.8% others. Regarding the significance factor evaluation, the result was 100% positive in antitumor activity, 84% positive in infection and inflammation pathology, 62% positive in others, like dental processes, food technology application support and as a drug absorption vehicle, and 50% in healing. The results presented in the current meta-analysis show that copaiba oil is an effective alternative to treatments of illnesses such as chronic inflammation, infectious diseases, various types of cancer, autoimmune diseases, and as a vehicle for the absorption of other drugs. Thus, more studies regarding the benefits of copaiba oil could provide a great contribution to the medical community in the treatment of the aforementioned illnesses.

## Keywords

- ▶ copaiba oil
- ▶ anti-inflammatory
- ▶ antimicrobial
- ▶ antitumor
- ▶ healing

## Introduction

A great number of Brazilian/Amazonian flora has shown to provide effective treatment for a multitude of ailments. One derivative of these plants is copaiba oil found in *Copaifera reticulata* Ducke, a natural product of the Amazon's biodi-

versity.<sup>1</sup> It has been used for more than 390 years as an anti-inflammatory, antimicrobial, and antifungal agent, and to prevent various types of cancer.<sup>2,3</sup>

Recent studies demonstrated that one of the major components of the copaiba oil,  $\beta$ -caryophyllene, has an anti-inflammatory effect.<sup>4</sup> Copaiba oil is extracted from the *copaifera*, a

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type of tree. Previous studies have claimed that copaiba oil, extracted from the copaibeira, could be found in more than 60 species cataloged worldwide.<sup>1</sup> However, in later studies it has been reported that there are currently 72 species of copai-beiras in the world, all exclusively in Brazilian soil.<sup>3</sup>

The anti-inflammatory and antimicrobial properties of copaiba oil have been drawing the attention of the scientific community as alternatives in the treatment for illnesses associated with inflammatory and infectious processes within the body.<sup>5</sup> Currently, the most common use of copaiba oil is topical.<sup>4</sup> Other, newer studies are being performed to find other forms of administration.<sup>6,7</sup>

In vitro experiments have shown direct damage to the DNA of cancerous stomach cells with the administration of copaiba oil. The responsible agent in copaiba oil was found to be kaurenoic acid. The administration of copaiba oil showed a reduction to the damage caused by cancerous cells in the stomach tissue during in vitro testing. This was due to the kaurenoic acid that makes up, in part, copaiba oil.<sup>8</sup> Likewise, the administration of nanoencapsulated copaiba oil significantly reduced the right ventricular hypertrophy of Wistar rats as well as the oxidative stress.<sup>9</sup> In another study, the administration of copaiba oil by gavage reduced the amount of abdominal adhesions and accelerated the formation of collagen fibers without damaging the early stages of healing.<sup>10</sup>

Although a large part of the studies showed positive results with the use of copaiba oil, a small part showed that copaiba oil did not show significant results in the applied objectives.<sup>3</sup> Tobouti et al affirmed that, reported that essential copaiba oil is a proven efficient medicine against some microorganisms. However, unlike other well established herbal medicines, antimicrobial studies on copaiba oil may show some bias due to lack of standardization. Therefore, the purpose of the present meta-analysis is to verify publications on copaiba oil and its uses as a therapy in the Pubmed/ Medline database between 2014 and 2017.

## Materials and Methods

The analyzed material consists of journal articles on the copaiba oil index in PubMed, seeking the relationship of copaiba oil with anti-inflammatory activity, antimicrobial activity, healing and antitumor effects. The data were collected between 2014 and 2017, totaling 42 items. The search for these articles was made using the keywords: *copaiba oil*, *anti-inflammatory*, *antimicrobial*, *antitumor*, and *healing*.

## Results and Discussion

In **Table 1**, we have found 42 articles published in the last 4 years, with 5 articles published in 2014, 16 articles

**Table 1** Scientific publications about copaiba oil between 2014 and 2017

| 2014 | 2015 | 2016 | 2017 | Total |
|------|------|------|------|-------|
| 5    | 16   | 7    | 14   | 42    |

This table shows the number of articles published each year.

**Table 2** Proposal of administration of copaiba oil according to the articles studied

|              | 2014 | 2015 | 2016 | 2017 | Total | %    |
|--------------|------|------|------|------|-------|------|
| Topical      | -    | 9    | 5    | 7    | 21    | 50.0 |
| Oral         | 2    | 3    | 2    | 5    | 12    | 28.6 |
| Enteral      | 1    | 2    | -    | 1    | 04    | 9.5  |
| Subcutaneous | -    | 2    | -    | -    | 02    | 4.8  |
| Others       | 2    | -    | -    | 1    | 03    | 7.1  |

published in 2015, 7 articles published in 2016, and 14 articles published in 2017. This shows a proportion of 11.9% of publications in 2014, 38.1% in 2015, 16.7% in 2016, and 33.3% in 2017. With this, we can observe a seasonality in copaiba oil research. Interestingly, there is an increase in publications in odd-numbered years when compared with even-numbered years.

In **Table 2**, we find a 50% proportion of copaiba administration in topical use in comparison to other administration methods. In 2014, we did not find any publication administering topical use. In 2015, there were 3 times more publications reporting on the topical use in relation to the oral use. By 2016, those numbers had fallen to nearly half as many. On the other hand, in 2017, we have found only 1.4 times more publications for the topical use as compared with the oral use. It seems that the oral administration of copaiba oil has been drawing attention in the last year due to its low toxicity and its antimicrobial and anti-inflammatory power.

These numbers initially demonstrate the potential of copaiba oil in the aid of the healing process.<sup>11,12</sup> Because of the benefits of applying copaiba oil as a topical use based on empirical evidence in the past, it is probable that the scientific community was influenced in researching the use of copaiba oil in the form most used by local Amazonian people, who used copaiba oil on the skin. According to Brito et al,<sup>13</sup> the practice of using medicinal plants is common in developing countries. The Amazon is a nursery of medicinal plants, and many studies have been made with copaiba oil as an alternative for aiding in inflammatory processes, such as healing skin ulcers and infections, with very satisfactory results in the form of topical use. According to Tobouti et al,<sup>3</sup> in 1840, copaiba oil was used in combination with purgatives for gonorrhea treatments, reporting that the treatment did not exceed 5 days, when the permanent cure of the disease was observed. This information was published by the Provincial Medical & Surgical Journal in a note written by the Gazette Médicale, and the Edinburgh Medical and Surgical Journal suggested a combination of copaiba with purgatives in the treatment of gonorrhea. Following this publication concerning the properties of the balsam, the copaiba has received attention from many explorers and travelers since the early years of its discovery.

The oral administration of copaiba has been used as another form of alternative therapy with controversial results. With 28.6%, in the present meta-analysis, the oral administration of copaiba has been shown to be an effective agent against certain parasites,<sup>14</sup> gastrointestinal cancer,<sup>8</sup>

endometriosis,<sup>6,7,15</sup> arthritis,<sup>16</sup> and other conditions. Contrary to what was thought, the oral administration of copaiba was shown to be non-toxic to rat liver when used as a carrier for amphotericin B.<sup>14</sup>

In contrast, in another study, the results revealed that copaiba oil showed anti-inflammatory and systemic antioxidant actions in arthritic rats. These beneficial effects, however, were counterbalanced by deleterious modifications in the metabolism and morphology of hepatic cells of healthy control rats. Thus, the administration of oral copaiba oil<sup>16</sup> demonstrates great potential as an alternative treatment to the aforementioned pathologies.

We can observe that the enteral administration by gavage was the third most used form in the present meta-analysis, with 9.5%. Campos et al<sup>9</sup> administered copaiba in natura and in nanoencapsulated form and both reported a significant reduction in the sizes of their right ventricles in induced pulmonary arterial hypertension (PAH). The same authors affirm that copaiba oil can be an alternative medicine for the reduction of hypertrophy of the right ventricle, as well as for the reduction of oxidative stress.

Researching the other copaiba administration routes, we have found the subcutaneous form to be effective 4.8% of the time, and other forms to be effective 7.1% of the time. According to Venturini et al,<sup>17</sup> the subcutaneous administration of copaiba in association with drugs for the treatment of carcinoma in the skin of pigs brought benefits by the increase in drug retention on the skin layer. The author states that copaiba is considered the most promising nanoformulation for the treatment of skin carcinoma by assisting the absorption of the drugs applied.

In ► **Table 3**, we can observe a predominance of the studies of copaiba oil as an antimicrobial agent with an effectiveness of 31%. As mentioned above, copaiba oil has been drawing the attention of the scientific community as an antimicrobial agent for a few years. According to Mizuno et al,<sup>18</sup> copaiba oil is one of the most popular natural medicines in the Amazon. The same authors reported positive effects in both antileishmanial activity as well as in antitrypanosomal activity with copaiba oil in topical administrations. In another study, Sventichny et al<sup>19</sup> demonstrated positive effects with antifungal activity in the administration of copaiba oil. Effects of antimicrobial activity have also been observed in many other studies, such as the inhibition of *Staphylococcus aureus*, as an antileishmanial agent,<sup>2</sup> the inhibition of *Staphylococcus agalactiae*,<sup>20</sup> and the inhibition of *Streptococcus sp.*<sup>21</sup> According Otaquiri et al,<sup>20</sup> the results of the antibacterial activity of

copaiba oil demonstrated a new alternative as a strategy in the control of *S. agalactiae* in neonatal infections. In another study, Alencar et al<sup>22</sup> showed significant antimicrobial and antibiofilm activities with the administration of copaiba oil, reporting it to be a promising candidate in the treatment of infections and in the incorporation of other antimicrobial drugs.

As with the antimicrobial activity of copaiba oil, the anti-inflammatory activity was present in the present study with 28.6% effectiveness. In a study to investigate the action of the oral administration of copaiba oil on the systemic inflammation, the oxidative status, and liver cell metabolism of rats with adjuvant-induced arthritis, Ghizoni et al<sup>16</sup> demonstrated that copaiba oil presented systemic anti-inflammatory and antioxidant actions in arthritic rats when compared with the control group. Lucca et al<sup>4</sup> attribute the anti-inflammatory action of copaiba oil to  $\beta$ -caryophyllene, a component of the oil. The anti-inflammatory action of  $\beta$ -caryophyllene is due to its agonist action at the cannabinoid receptors known as CB2.<sup>23</sup> Thus, the anti-inflammatory activity of copaiba oil occurs because  $\beta$ -caryophyllene binds selectively to CB2 receptors, being a CB2 agonist.<sup>31</sup> When this occurs, there is an inhibition of adenylate cyclase, triggering a cascade of biochemical reactions that contribute to the systemic anti-inflammatory activity.<sup>23</sup> Likewise, Teixeira et al<sup>1</sup> reported an increased efficiency in the modulation of inflammatory processes, mainly in the number of macrophages observed. According to the author, therapies with copaiba oil have been shown to be of low toxicity when administered in the oral form.

Another purpose of copaiba oil that drew attention in the present study was its antitumor action, with 9.5% of the studies finding that copaiba oil demonstrated a high antitumor capacity. In a study on gastric cancer, Cardoso et al<sup>8</sup> demonstrated that the administration of caurenoic acid, extracted from copaiba oil, significantly reduced mitosis in gastric cancer cells by inducing apoptosis in these tissue types when compared to the control group. However, Cavalcante et al<sup>24</sup> demonstrated a genotoxicity in the use of kaurenoic acid using 2.5, 5, 10, 30, and 50  $\mu\text{g/mL}$  in lung fibroblast cells of hamsters. Likewise, Ghizoni et al<sup>16</sup> reported that although copaiba oil showed positive results in the treatment of inflammations at doses between 0.58 and 1.15 g/kg, detrimental changes were found in the liver metabolism and in the liver morphology. Interestingly, in another study, Campos et al<sup>25</sup> demonstrated that the use of trans-caryophyllene extracted from copaiba oil associated with atorvastatin presented significant leukocyte counts compared with the control group in chemotherapy treatments in Wistar rats, reporting a potential preventative effect for secondary leukopenia in induced chemotherapy. These differences in toxicity reported in the use of copaiba oil were even more evident when Teixeira et al<sup>1</sup> demonstrated that 200 mg/kg/day presented low toxicity and positive results in inflammatory processes. Similarly, Silva et al<sup>6,7</sup> demonstrated that 50  $\mu\text{g/mL}$  of nanocomposite system (Nano COR) was developed and a toxicity test was performed. The tests showed that Nano COR has a greater impact on the behavior of human endometriotic stromal cells than on the behavior of eutopic endometrium stromal cells, supporting the idea that Nano COR, a form of copaiba oil, should be further investigated

**Table 3** Objectives of research on the use of copaiba oil

|                   | 2014 | 2015 | 2016 | 2017 | Total | %    |
|-------------------|------|------|------|------|-------|------|
| Antimicrobial     | 1    | 7    | 2    | 3    | 13    | 31.0 |
| Anti-inflammatory | 3    | 4    | 2    | 3    | 12    | 28.6 |
| Antitumor         | –    | 2    | –    | 2    | 4     | 9.5  |
| Healing           | –    | 1    | 1    | 2    | 4     | 9.5  |
| Others            | 1    | 2    | 2    | 4    | 9     | 21.4 |

**Table 4** The results with significance, evaluated

|                             | 2014     |          | 2015      |          | 2016     |          | 2017      |          | Total %     |             |
|-----------------------------|----------|----------|-----------|----------|----------|----------|-----------|----------|-------------|-------------|
|                             | Positive | Negative | Positive  | Negative | Positive | Negative | Positive  | Negative | Positive    | Negative    |
| Cancer                      | -        | -        | 2         | -        | -        | -        | 2         | -        | 100.0       | -           |
| Infections and inflammation | 3        | 1        | 10        | 1        | 3        | 1        | 5         | 1        | 84.0        | 19.0        |
| Others                      | -        | 1        | -         | 2        | 2        | -        | 3         | -        | 62.5        | 37.5        |
| Healing                     | -        | -        | -         | 1        | 1        | -        | 1         | 1        | 50.0        | 50.0        |
| <b>Total</b>                | <b>3</b> | <b>2</b> | <b>12</b> | <b>4</b> | <b>6</b> | <b>1</b> | <b>11</b> | <b>2</b> | <b>78.0</b> | <b>22.0</b> |

as a novel and valuable alternative to treat endometriosis. These controversies between the toxicity of copaiba oil and of its components still require further study. Perhaps a dose adjustment by weight is a path in the search for a safer treatment with a product as promising as shown in ►Table 4.

We have reviewed the pertinent articles to evaluate the healing properties of copaiba oil. A curious fact is that, empirically, in the past, native Amazonians used copaiba oil for healing. However, in the present study, we have observed that only 9.5% of the publications aimed to study this property. Thus, we have looked at some works with copaiba oil administered via gavage for abdominal adhesion in rats corrected with Vicryl (Ethicon Inc., Somerville, NJ, USA) mesh.<sup>26</sup> The authors demonstrated that although the gavage administration showed no statistically significant difference in adhesions and collagen fibers, the inflammatory response was better in the group that used copaiba oil. Copaiba oil also showed positive effects on bladder healing,<sup>11</sup> and skin healing processes.<sup>27</sup>

In ►Table 5, we see a predominance of in vitro research, with 50%, followed closely by the publications of clinical studies in animals, with 40.4%. In the papers evaluated in the present meta-analysis, we could see that copaiba oil is promising in the medical field as a very great potential alternative therapy as an antimicrobial,<sup>19</sup> anti-inflammatory,<sup>1</sup> as well as an antitumor agent.<sup>17</sup> These numbers show that, until now, the researchers working with copaiba oil seem to want to corroborate the empiric act of the local natives with the use of this medicinal plant.

On the other hand, human studies are still lacking to validate the therapeutic effects of copaiba oil. The publications with human subjects corresponded to only 2.4% of the works evaluated in 2017. Observing the anti-inflammatory

**Table 5** Publication types

|                 | 2014 | 2015 | 2016 | 2017 | Total | %    |
|-----------------|------|------|------|------|-------|------|
| In vitro        | 1    | 10   | 6    | 4    | 21    | 50.0 |
| In vitro animal | 3    | 7    | 1    | 6    | 17    | 40.4 |
| In vitro human  | -    | -    | -    | 1    | 1     | 2.4  |
| Review          | -    | -    | -    | 1    | 1     | 2.4  |
| Others          | 1    | -    | -    | 1    | 2     | 4.8  |

potential of copaiba oil, we believe that in the coming years the scientific community will focus more on publications with humans, especially in the sports field, because the inflammatory processes in sports, such as tendinitis, muscular contractures, stretching, and dislocations, are very common. However, we must not forget the elderly, who also present with a high incidence of inflammatory processes due to their age.

Regarding the publications in review form, we have found the same percentage of clinical studies in humans, which was of 2.4%. Of these, 4.8% were studies on the chemical composition of copaiba oil.

In ►Table 4, we can observe the comparative results presented in these 42 studies on the administration of copaiba oil. With 84% of positive results and inflammation, copaiba oil has been shown to have a therapeutic potential for both conditions. Controversial results still appear because of the great diversity of copaifera that exists in various parts of the continent. According to Tobouti et al,<sup>3</sup> in the scientific literature about copaiba oil, many articles do not specify which exact strain is being studied. This makes it difficult to compare results between studies. Studies with  $\beta$ -caryophyllene present in copaiba oil have been demonstrating its anti-inflammatory properties and its therapeutic effects.<sup>4</sup> Therefore, the use of copaiba oil extracted from trees with low  $\beta$ -caryophyllene concentration may compromise the results of the studies.<sup>3</sup>

Another component from copaiba oil with potent antioxidant and anti-inflammatory properties is kaurenoic acid.<sup>6,7</sup> According to Silva et al<sup>16</sup>, the results of their research demonstrated a significant decrease in tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and Interleukin-1 (IL-1) expression and myeloperoxidase (MPO) activity at the T1/T2 time point.

In the results reported by other studies with copaiba oil, there are uses of copaiba oil as a vehicle for administration of medicaments, for topical and oral treatment<sup>28,29</sup>, in food technology<sup>30</sup>, dental procedures<sup>30</sup>, and cardiorespiratory processes.<sup>9</sup> Here we can observe a positive result in the use of copaiba oil of 78% according to ►Table 4. This can demonstrate versatility in the use of copaiba oil for different purposes.

In the studies using copaiba oil with a focus on its antitumor action, the results were promising. Of the 4 studies published in the database that were collected for the present meta-analysis, 100% of the results showed a decrease in tumor activity in the presence of copaiba oil in any form of

administration, whether oral, topical or in vitro. Although we have found few studies on antitumor activity in our present study, the use of copaiba oil in cancer therapies have shown great results. Further clinical studies with copaiba oil in humans are required for future development of dosages, toxicity, and pharmacokinetic and pharmacodynamic activities.

Interestingly, differently from the results on antitumor activity, the percentages presented with respect to the healing properties of copaiba oil were different than expected, with only 50% of positive results found. Considering the empirical use of local people in the use of copaiba oil as a healing agent, this result was a surprise. However, we cannot fail to report that the studies found on the healing properties of copaiba did not involve its application oil on the skin exclusively. Yasoshima et al<sup>26</sup> used copaiba oil via gavage in rats that underwent hernia repair with Vicryl mesh. According to the authors, there were no significant results in the postoperative healing process when compared with the control group. Wagner et al<sup>12</sup> used copaiba oil in local ulcers in the mouth of rats and did not obtain significant results.

## Conclusion

The proposed administration of copaiba oil in pathological processes seems promising. The results presented in this meta-analysis show that copaiba oil is an interesting alternative for treatments in pathologies such as chronic inflammation, infectious processes, various type of cancer, autoimmune diseases, and as a vehicle for the absorption of other drugs. However, more studies on copaiba oil would bring a great contribution to the medical community in the search for alternative treatments. We have not found studies related to age-fighting properties of copaiba oil. Therefore, there is an open gap here.

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