Chapter 54

Clinical utility of essential oils in women's health for phytotherapeutic treatment of candidiasis: a systematic review with emphasis on the potential of copaiba oil (Copaifera sp) from Brazilian biodiversity and technological perspectives applied to biomedicine

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ABSTRACT
The clinical application of essential oils has been prospected in recent years from the results of experimental laboratory tests, including the verification of antimicrobial and anti-inflammatory action. Brazil is one of the largest producers of essential oils and has in its megabiodiversity an alternative of institutional, social, environmental and economic development, considering the necessary and current perspective of strengthening the sustainability agenda. In Brazil, vulvovaginal candidiasis is the second most frequent type of vulvovaginitis that affects women's health, and is caused by the fungus *Candida albicans*. This is an organism from the resident microbiota of some organs and that, in excess, causes an uncomfortable clinical picture, capable of drastically affecting the patient's daily life, which makes its effective treatment of utmost importance. As essential oils (EOs) from medicinal plants have shown potential efficacy and reduced side effects, their use as a possible herbal medicine for clinical purposes against candidiasis should be explored. The aim of this study was to elucidate scientific evidence on the use of EOs from plant species, with emphasis on Copaiba oil from Brazilian biodiversity, and its antimicrobial activity against Candida. It is expected to have subsidies regarding safety and efficacy for clinical trials in patients with vaginosis, since there are currently gaps in knowledge about these indicators. In this systematic review study, electronic searches of articles in the CAPES, Pubmed, SciELO and LILACS databases were carried out, using as inclusion criteria in vitro (anti-culture) and in vivo studies (clinical and/or pre-clinical trials) that addressed the use of EOs, their phytochemical constituents and comparative Azo Groups as fungistatic drugs, Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of the EO, Cytotoxicity tests and effects of the EO against fungal infections in animals. EOs were found to be effective as a treatment, especially in strains resistant to the usual drugs, and no adverse reactions, toxicity or changes in formation were identified in in vitro tests performed on pregnant and non-pregnant mice. The copaiba oil (*Copaifera* sp), present in the rich biodiversity of the Brazilian flora, presents satisfactory antimicrobial action against *C. albicans*

and with absence and/or low toxicity in certain conditions, being a relevant indicator for clinical tests. Other essential oils native to Brazil and/or originating from exotic useful plants present phytotherapeutic potentials. It is necessary and urgent the advance in learning and adopting digital technologies, especially in research involving epidemiological and/or clinical data, in order to substantiate the decision making in terms of public health policies. As perspectives of microbiological assays and clinical tests with essential oils, as in the case of this study, there are still gaps in the development of studies carried out, where the use of digital technology is certainly an increasingly urgent need due to the relevance of agility in research protocols, methodological procedures and analysis of their results. Universities, either through undergraduate or graduate courses, as in areas of knowledge such as biological and health sciences, either medicine, pharmacy or even information technology and engineering, such as biomedical engineering, among others, urgently need to strengthen the area of digital technology and innovation in the teaching-learning process and knowledge practices. The research funding agencies, whether public or private, need to give special attention to the technological era for research, laying a more dynamic foundation for decision making and the implementation of sectoral public policies.

Keywords: Copaiba Oil, Phytotherapy, Vulvovaginal Candidiasis, Clinical Research, Technology, Biomedicine.

1 INTRODUCTION

The clinical application of essential oils is the target of recent studies in the world and in Brazil, due to their potential applications for human health, above all. Brazil is one of the largest producers of essential oils and has in its megabiodiversity an alternative of institutional, social, environmental and economic development, considering the necessary and current perspective of strengthening the sustainability agenda. There is an interest in research with microorganisms, in view of the resistance to common drugs due to the recurrent use and the aggravation of certain pathologies, with failure to conventional drugs, in addition to the potential of native flora, still little investigated from the point of view of clinical use in humans and in a safe and effective way. The microorganism Candida albicans is a fungal species that is part of the resident microbiota of some organs such as mouth, esophagus and vagina, however, due to its opportunistic character, it can cause serious infections in some conditions, such as host immunosuppression (Tortora et al., 2017). Among such infections, vulvovaginal candidiasis is the second most common vulvovaginitis, being a frequent cause of gynecological consultations (Fontana, 2009; Muniz et al., 2019). It can become recurrent in some patients, being a problem of paramount public health importance due to the fact that it affects a representative number of women and causes discomfort due to the clinical manifestations presented, such as intense pruritus, leukorrhea and sexual dysfunction (Muniz et al., 2019; Queiroz Filho, 2013; Gunther, 2014).

In recent years, interest in natural medicines, essential oils and other phytotherapies has increased in response to the increasing incidence of side effects associated with conventional drugs and the emergence of Candida resistance to antibiotics (Mondello et al., 2003), largely due to inappropriate use of drugs, which has led to a deficit in the good results of candida treatments in general. Resistance of microorganisms to treatments leads to the use of more broad-spectrum drugs, which generally cause more undesirable effects (Castro, 2006).

Plants are sources of raw materials for obtaining biologically active compounds, and many have become references for the synthesis of widely used drugs (Simões et al., 2010). Studies involving phytotherapeutics, among them essential oils, oil resins and isolated components have shown promising results for the treatment and prophylaxis of fungal infections, including in strains resistant to conventional antifungal drugs (Mondello et al., 2003; Deus et al., 2011). The use of medicinal resources from plants is one of the oldest medicinal practices, however, many are used with little evidence and sometimes no concrete information for their use (Veiga Junior; Pinto 2002), which can bring harm to those who use them, taking into account the cytotoxic and carcinogenic potential of some substances from plants (Chacon et al., 2002).

A recent study developed by Vieira et al. (2019), by analyzing the chemical composition and cytotoxicity of essential oils from herbal plant and exotic species, point out the need for the development of specific in vivo studies and clinical trials on the safety and efficacy of essential oils, to evaluate the practical relevance of the results obtained in vitro for the future development of new products with possible therapeutic applications.

In the Brazilian flora, the genus Copaifera belongs to the large and leafy trees, especially present in the Amazon, Cerrado and Atlantic Forest biomes. These plants are popularly known as copaibeira, copaívas or pau-de-leo and belong to the Fabaceae family, comprising a worldwide representativeness of about 70 species, of which 16 occur in Brazil (Arruda et al., 2019). Among the therapeutic alternatives, using medicinal plants of wide popular knowledge, the oil of the copaiba genus is potential and whose biodiversity is abundant in the Brazilian territory, native trees being found in the Southeast, Midwest, North and Northeast regions (Azevedo, 2004). The oil in the consistency of "resin oil" results from the extraction in the trunk of the plant through drilling and collection (Oliveira, Lameira and Zoghbi, 2006). Studies prove the effects of Copaifera sp against multidrug-resistant bacteria (Abrão et al., 2015), anti-inflammatory (Pacheco, 2006), healing (Montes et al., 2009) and antitumor (Cunha, 2006; Abrão et al., 2015) and antimicrobial (Deus et al., 2011; Santos, 2008).

Recent studies developed by Símaro et al. (2021) with cells in vitro highlighted that the oil of Copaifera pubiflora Benth does not present cytotoxicity and with anti-inflammatory and antinociceptive action of the oleoresin whose major metabolite was ent-hardwíckiic acid, showing the prevention that the organism produces cytokines which are proteins that regulate inflammation, requiring more studies, especially clinical studies, since Brazil produces about 600 tons per year of the oleoresin of Copaíba sp, which are sold worldwide for the production of various products applied in the industry applied to health.

The essential oils (EOs) have shown relevant biological antifungal activity, including those derived from copaiba, conferring potential for alternative therapeutic solution to conventional drugs used in SUS, for the treatment of vaginal infections caused by the microorganism of the candida genus. However, studies

are still scarce, especially on indicators of efficacy and safety, basic requirements of the phytotherapeutic, which justifies this study whose objective was to elucidate the scientific evidence of the use of essential oils of plant species, with emphasis on the oil of copaiba, and its antimicrobial activity against Candida sp seeking subsidies on safety and efficacy for clinical trials. There are herbal medicines based on copaiba oil and marketed in Brazil, however, there is no knowledge of studies that guarantee the efficacy and safety of the use of this oil to combat candida. It is relevant the deepening of studies through the future perspectives on the provision of an effective phytotherapeutic, affordable and desirable that is available nationally by SUS (Unified Health System). This is because, since 2006, the Ministry of Health has made therapeutic and preventive options available to users of SUS, among them the use of medicinal plants and herbal medicines, which has led many Brazilian cities and states to implement phytotherapy in their primary health care networks. The herbal medicine service is offered in 1,108 Brazilian municipalities, according to 2017 data from SISAB - Health Information System for Primary Care. In Brazil, the Brazilian Phytomedicine Association - SOBRAFITO, founded in 2003, reinforces the need for research involving plants as medicines, as it considers that their use is based on safety and efficacy, providing SUS doctors especially with one more option for disease treatment.

2 MATERIALS AND METHODS

Study Type and Research Strategy

This is a study of the Systematic Literature Review type whose search strategy adopted by two of the authors, consisting of conducting an electronic search from the combination of the terms: "Vulvovaginal candidiasis" AND "Essentials oils" AND "pre-clinical trials" OR "clinical trials" OR "in vitro tests" OR "laboratory assays" OR "copaifera". The databases used were portal of institutionalized journals in Brazil, being CAPES, Pubmed, SciELO and LILACS, seeking to substantiate the discussion of the theme by also using other scientific productions published between 2019 and 2022 in English language and international journals of access and open base on line for viewing either the abstract or in full, published between 2019 and 2022, in order to answer the following question generating the study from the use of the methodology and strategy PICOS (acronym for P: population/patients; I: intervention; C: comparison/control; O: outcome/outcome): "Are there scientific evidence and in vitro and in vivo experimental data regarding the efficacy and safety of the use of essential oils against C albicans, including copaiba oil (Copaifera sp) present in the rich Brazilian biodiversity, being potential herbal medicines and of clinical utility for vulvovaginitis, a recurrent pathology involving women's health?

Inclusion Criteria

In vitro (anti-culture) and in vivo studies (clinical and/or pre-clinical trials), written in Portuguese and English and with free and open access, via online, were included, and that related important efficacy and safety signaling points: (1) the use of Essential Oils (EO); (2) their phytochemical constituents (majority and/or secondary metabolites) that account for antifungal activity to Candida albicans strains; (3) comparative EO and Azois Groups of commercial antifungal drugs; (4) Minimum Inhibitory Concentration (MIC) of EO, (5) Minimum Fungicidal Concentration (MIC) of EO; (6) cytotoxicity tests; (7) effects of EO on fungal infections in animals and (8) biological tests used cells and major secondary metabolite isolated from copaiba oil.

Exclusion Criteria

Studies were excluded that did not report the use of EOs from herbal plants; or that did not combat fungi exclusively of the Candida genus; or did not do antifungal tests; or were not related to the medical field; as well as Review and gray literature articles.

Study Selection

The identification and screening of the scientific production to be systematized was done by two authors who evaluated the title and abstract of all articles found in the search strategy, independently. Those that presented any relation with the inclusion criteria were evaluated in their entirety to verify total compliance with the criteria. The doubts in the analysis of the abstract and/or the full text were solved by a third author, resulting in the selection of the eligible scientific production for systematization of the results and analysis, prioritizing the methodology of the acronym PICOS for the systematic review type study.

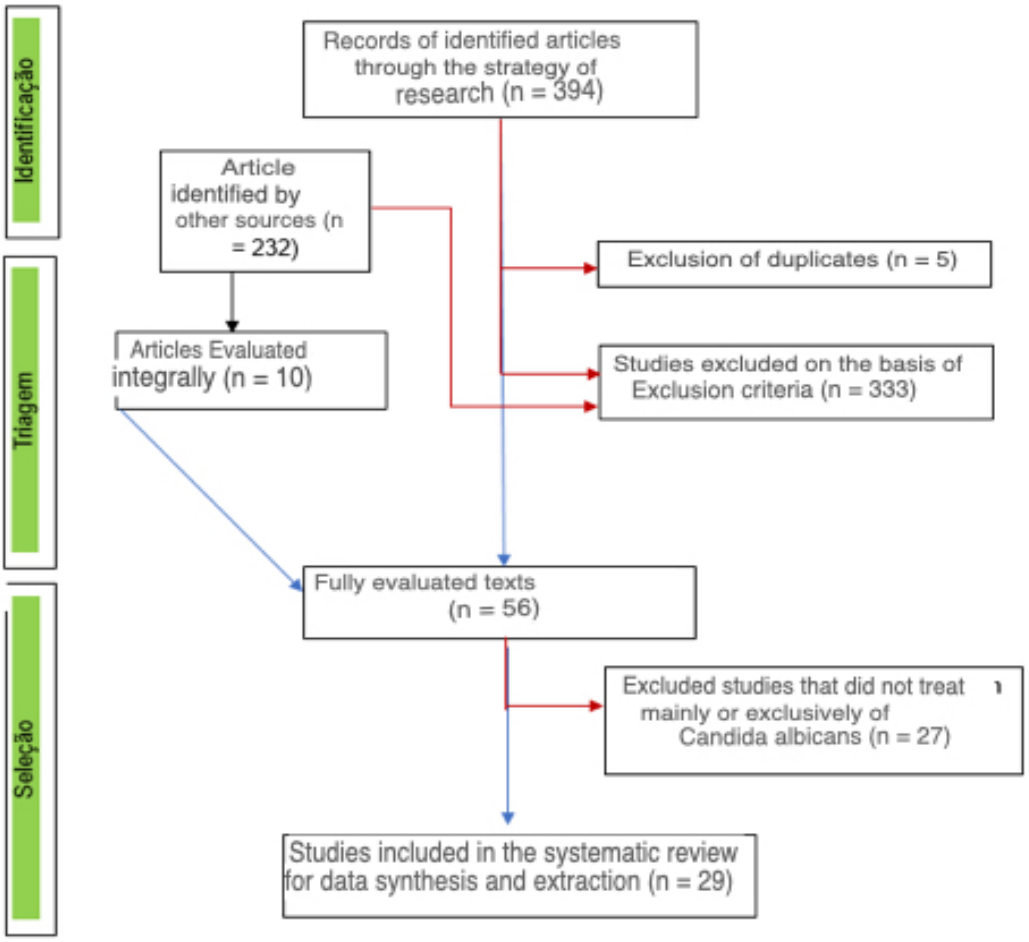
Data Extraction

Four standard tables were prepared from the information in the articles, the first focusing on in vitro studies, the second on in vivo studies, and the third on copaiba oil. The variables were: (1) author and year of publication; (2) type of study and when it was an in vivo study it was mentioned whether or not it had approval from the Animal Ethics Committee or Ethics Council involving human beings and the oil used; (3) evaluation showing the chromatographic profile and the components of the oil studied, the minimum concentration and the prophylaxis and therapeutics when present; (4) conclusion, effectiveness or otherwise of the EOs in the tests done against fungal infection.

3 RESULTS AND DISCUSSION

From the identification of three hundred and ninety-four (394) scientific texts indexed in the accessed databases, twenty-nine (29) were selected, according to Figure 1, meeting the criteria and the intended objective of the present study.

Figure 1. steps in the selection process of in vivo and in vitro studies with essential oils with emphasis on clinical utility of essential oils in women's health, including copaiba oil (Copaifera sp), c as potential herbal medicines against Candida sp microorganism.



In vitro studies against Candida albicans infections: essential oils and their efficacy

From the results summarized (Table 1) from studies conducted in vitro we can highlight important aspects indicative of the efficacy of essential oils for therapeutic purposes against Candida infections.

Romano et al. (2005) investigated the in vitro activity of three bergamot oils (natural essence, furocoumarin-free extract, and distilled extract) against Candida species. Importantly, all 3 isolated components exerted antifungal activity, however, the distillate (DE) was superior to the others, it had volatile residues, followed by the furocoumarin-free extract (FF), free of volatile residues, the phototoxic bergapten.

The studies by Hammer et al. (2000), analyzed in vitro germination tube growth (CTG) of Candida Albicans, under the effect of tea tree oil (TTO). The evaluation was based on MIC (Minimum Inhibitory Concentration) and CFM (Minimum Final Concentration), obtaining good response in both. In 1988, the same authors had already performed an in vitro study of MIC and MFC with 114 Candida spp strains susceptible to TTO, comparing it to other oils such as bergamot oil, oregano, pepper, santolia, coriander, among others.

Ergin-Arikan-Akdagli (2002), analyzed the in vitro activity of fluconazole against vaginal candida, as well as determined the in vitro activity of tea tree oil (TTO), whose main constituents and respective concentrations were terpinen-4-ol (40.8%) and 1,8-cineol (2.8%), against cases that are resistant to fluconazole. A total of 99 candida strains were isolated from vaginal culture; the MIC result varied for the different strains studied, being for C. albicans and C. krusei a range of 1-4% and for C. glabrata and C. parapsilosis a range of 0.5-2%; for fluconazole the MIC result was within the expected range.

D'Auria, et al. (2005) evaluated in vitro the main components of lavender oil (linalool and linalyl acetate) against the growth and formation of the germ tube of Candida, which uses it for dissemination. In their study, the strains were analyzed in both vaginal and oropharyngeal infections; regarding minimum inhibitory concentrations (MIC), all lavender, linalool, linalyl acetate, miconazole, ketoconazole, fluconazole oils were more effective in oropharyngeal infections; As for the minimum fungicidal concentrations (MFC), superiority also occurred in oropharyngeal infections; however, linalin acetate and fluconazole showed equal percentages for both infections. As for cytotoxicity, lavender oil 0.5% killed 98% of cells in 30 minutes, linalool 0.5% killed 100% of cells in 30 seconds, linalyl acetate 2% killed 93% of cells in 30 minutes.

As for the studies that sought to characterize the chemical constituents of the oleoresin of Copaifera duckei, Maistro, et. al. (2005), evaluated concentrations (10%, 25% and 50%) and its mutagenic and cytotoxic potential by applying the micronucleus test in peripheral blood and analysis of chromosomal aberrations in bone marrow cells of wistar rats, both sexes, treated with this oleoresin. Three groups were selected: mean number of micronuclei in reticulocytes (NMMR) of peripheral blood; mitotic index; mean number of chromosomal aberrations (NMAC); as for the first assay of (NMMR) of peripheral blood, there were no statistically significant differences, the mitotic index in the 25% and 50% concentrations of oleoresin showed a significant decrease ($p<0.05$ and $p<0.01$ respectively). NMAC there were no statistically significant differences between the three experimental groups and the negative control group.

In vivo studies against Candida albicans infections: Essential oils and their efficacy

The systematized results of pre-clinical studies involving animal experimentation (Table 2) point to the use of essential oils, such as Santolina Chamaecyparissus (Suresh et al., 1997) and Progostemon cablin

(Li et al, 2012) as combating vulvovaginosis as well as in more recent studies involving carcinoma patients aiming to combat oral candidiasis by the use of Punica granatun, popularly known as Pomegranate (Santos et al.,2017), culminating in possibilities of effective treatments against C. albicans.

Two studies developed by Mondello et al. (2003 and 2006) were selected based on the action of essential oils, isolating the main constituents against strains of C. albicans. The first study, in 2003, analyzed the antifungal action of tea tree oil (TTO)/Melaleuca alternifolia in vitro and in vivo, administered intravaginally, after infection on 101 isolated strains of Candida sp and 14 of Cryptococcus neoformans susceptible and resistant to antifungal agents, in Wistar rats, showing excellent biological activity being: in the in vitro experiment TTO inhibited the growth of all isolates tested, including those resistant to fluconazole and itraconazole; while in vivo TTO for C. albicans susceptible to one of the widely used azole drugs, fluconazole, exerted a statistically significant decrease in colony forming unit (cfu) counts in the first 2 weeks and rapid elimination of the fluconazole resistant strain.

Already in the second study, Mondello et al (2006) analyzed the Australian Melaleuca alternifolia (Maiden and Betch) Cheel oil comparing with a stock solution of fluconazole and a stock solution of itraconazole (ITC) and investigating the activity in vitro and in vivo, where in this case the administration was intravaginal of two critical bioactive constituents of Melaleuca alternifolia Cheel oil (TTO) terpinen-4-ol and 1,8-cineol. There was satisfactory action, i.e. the results obtained with fluconazole susceptible C. albicans strain (FLC), as well as terpinen-4-ol (1% v/v) which exerted a marked acceleration of yeast clearance. In addition, terpinen-4-ol (1% v/v) also caused a rapid clearance of the FLC-resistant strain from the vagina of experimentally infected mice.

Chami, et al. (2004), evaluated in vivo, administered intravaginally in 54 Wistar rats the anticandidal activity of the carvacrol and eugenol components of the essential oils of the popularly known herbs oregano and clove against several strains of C. albicans. This was a histological and microbiological study of carvacrol (C), eugenol (E) and nystatin (N), so they were able to differentiate prophylactic treatment from therapeutic treatment. The 54 rats were tested histologically and microbiologically. However, there was a division into 6 groups of 9 rats, 27 tested for the microbiological-pophylactic effect for each of the compounds (C), (E), (N) and the other 27 tested for the microbiological-therapeutic effect also for the three compounds (C), (E), (N). Similarly proceeded the prophylactic and therapeutic division for histological study; regarding the first effect, all three compounds showed significant reduction in colonization and elimination of vaginal infection by day 10. Regarding the second effect, 7 of the 9 rats tested with the (C) had negative culture. And 7 out of 9 tested for (E) remained infected, while for nystatin only 1 out of 9 rats remained infected. In the histological data: both in the prophylactic and therapeutic treatment, no candida was found in the vaginal lumen in the histological sections made in the animals of the three groups.

Therefore, there is scientific evidence demonstrating the efficacy of these oils in the tested antifungal action under experimental conditions.

The anti-inflammatory action resulting from Cadidiasis and Vaginosis caused by G. vaginalis was evidenced in two relevant studies. Maruyama et al. (2008) analyzed a method of application of essential oils such as Geranium, in vitro and in vivo, where solutions were injected vaginally against the growth of Candida albicans resulting in: essential oils such as clove, oregano and lemon grass without the addition of clotrimazole, a synthetic antifungal, were not effective against C. albicans. Geranium oil, associated with vaginal washing and in the dosage of 25 to 50 mg/ml prevented the growth of mycelial forms and above 100 mg/ml prevented the growth of yeast forms, however, there was a window of inactivity against these yeasts in the dosage of 6.25 to 100 mg/ml, by Geranium oil, which evidences the influence of the dose on the effectiveness of the antifungal.

Trinh, et al. (2011) investigated the inhibitory effects of Artemisia princeps pamp (AP), Asteraceae family, essential oil (APEO) and its main constituents against bacterial vaginosis and vulvovaginal candidiasis. AP and APEO essential oil were efficient in inhibiting the growth of G. vaginalis and C. albicans by suppressing the inflammatory response of their constituents.

These authors emphasize that intravaginal treatment with APEO, eucalyptol or α-terpineol significantly inhibited G. vaginalis counts by 81% and myeloperoxidase activity in vaginal tissues by 78% compared to untreated controls. Topical treatment with APEO, eucalyptol or α-terpineol significantly reduced viable C. albicans counts in the vaginal cavity by 62% and myeloperoxidase activity by 64% compared to untreated. In isolation, α-terpineol activity suppressed expressions of IL-1β, IL-6 and TNF-α, and eucalyptol and α-terpineol negatively regulated COX-2 and iNOS expressions and NF-κB activation in macrophages. And most importantly neither eucalyptol nor α-terpineol, had cytotoxic activity. Such studies show that certain essential oils through the evidence of in vivo and in vitro studies do not have side effects, which increases the expectation of its phytotherapeutic applications.

Copaíba resin oil, antifungal action against C. Albicans isolates and phytotoxicity: evidence from pre-clinical studies

The selection of four scientific articles addressing the antimicrobial action against the fungus C. albicans as well as analyzing the effect of safety related to phytotoxicity or not (Table 3) allowed the following inferences: that the oil of copaiba resin (Copaifera sp) is an alternative herbal medicine, given the antimicrobial action against C. albicans. albicans; and that according to Deus et al. (2011) it was necessary to conduct more specific studies in the fight against candidiasis, which, nowadays, has been revealed according to Lima et al. (2017) when evaluating as positive the subacute treatment with oil-resin of copaiba, used both orally and intravaginally in rats, causing no clinical signs of toxicity.

Among such studies, Lima et al. (2011), in previous studies evaluated the reproductive performance, at preclinical level, of animals treated with vaginal cream and intravaginal route containing oil of copaiba (Copaifera duckei Dwyer) resin. Male, female, and albino rats of the Wistar strain weighing around 250 g were used. The main focus was the weight, and the appearance of anomalies in pregnant rats and fetuses, obtaining very promising results regarding the safety of a possible phytotherapeutic drug, due to the non-toxicity in subacute treatment with resin oil administered orally and intravaginally: in maternal weight no visible clinical signs; in reproductive performance the female group had a full-term pregnancy; in fetal weight most of them were adequate for gestational age; as for implantation and resorption sites there was no significant difference between the groups; and as for external and internal anomalies and malformations no malformations or external anomalies were diagnosed in the control group. It is important to highlight that depending on the concentration, it is known that essential oils may respond differently regarding efficacy and/or toxicity, which Tobouti et al. (2016) point out that in 10% of C. officinalis oil there was significant inhibition of C. albcans biofilm adhesion by the EO, indicating biological activity against the fungus.

It is relevant to emphasize a little more the contributions of the most recent study developed by Lima et al. (2017), where they evaluated the toxic effects in subclinical treatment, based on the application of copaiba oil-resin vaginal cream. In that study, 35 animals were subdivided into 2 groups: one with 20 and the other with 15, with the following subdivision; 20 animals were divided into two groups (n = 10 /group, five males and five females) and treated orally with C. duckei oil-resin and distilled water (ORC and Control). Another 15 animals (females) were divided into three groups (n = 5 /group), which received intravaginal treatment with C. duckei oil-resin vaginal cream (CVC), C. duckei oil-resin only (ORCV) and the control group, with the vaginal cream), basic (CVC control). They also evaluated the weight of the animals; hematological evaluation: leukocyte count, hematocrit, hemoglobin. Thus, no death and no signs of toxicity were observed in the subclinical treatment with oil-resin and C. duckei (CVC).

The resin oil of Copaifera ducke, according to Maistro et al. (2005) showed cytotoxic effects at high doses, but did not induce a statistically significant increase in the mean number of chromosomal aberrations or the mean number of micronuclei in peripheral blood reticulocytes of Wistar rats in vivo, so despite the cytotoxic effect it is non-mutagenic.

Menezes, et. al (2008), evaluated in vitro the antifungal activity of essential oils and extracts, present in the Amazon region among the essential oils is: Copaífera multijuga (copaiba) on the main strain of Candida albicans. In addition, they determined the minimum inhibitory concentration of the oils and extracts that showed antifungal activity. Copaífera multijuga oil did not show efficacy against C. albicans.

According to Deus et al. (2011), the halo of inhibition caused by the use of Copaifera multijuga Hayne oil and Miconazole Nitrate against the action of C. albicans, demonstrated range of efficacy, which

according to the authors, occurs when a percentage equal to or greater than 85% show good potential antimicrobial action for practical uses of Copaifera multijuga Hayne against candidiasis.

Another relevant information refers to the phytochemical marker possibly influencing such antimicrobial responses of Copaifera multijuga Hayne oil-resin, being transcaryophyllene, chemical compound present in the sample according to Lima et al. (2011). In this study, treatment with the vaginal cream containing copaiba resin oil did not affect maternal weight at any stage of gestation. Thus, it did not interfere with reproductive performance during pregnancy at the dose tested, and did not affect the appearance of external anomalies and/or malformations.

Regarding the comparison with azois drugs, it is important to highlight some studies. God et. al (2011) when evaluated the antifungal potentials of the resin oil (OR) and the (OE) of copaiba (Copaifera multijuga Hayne), comparing their levels of fungitoxicity with Miconazole Nitrate (NM), against 5 species of fungi of the genus Aspergillus and 3 of yeasts of the genus Candida. Main compounds: α-copaene, β-caryophyllene, Trans-α-bergamotene, α-humulene, ɤ-muurolene and β-bisabolene. As for the Inhibition halo (mm) of (OR) Candida sp.: 7.0 - 9.0; (OE) Candida sp.: 9.5 - 16.0; (NM)- Candida sp.: 10.0 - 15.0. MIC (mg mL-1), (OR): Candida sp.: 0.3 - 0.6; (OE) Candida sp.: 0.1 - 0.5; (NM): Candida sp.: 0.1 - 0.5. Apparently the EO showed a very similar halo of inhibition and MIC to the NM.

It is important to highlight the study by Mirza et al. (2013) because, although it is not related to copaiba oil, it addresses a therapeutic option in the form of a gel whose base also comes from essential oil, Tea Tree Oil (TTO), probably being possible to adapt to copaiba oil. These authors produced a thermosensitive, stable gel, based on Tea Tree Oil (TTO) and Itraconazole (Itz), and observed its synergistic effect, the action of the two together, in combating recurrent vulvovaginal candidiasis (CVVR) in 18 wistar rats, administered in gel form, for this they analyzed: "Tea tree oil" - (TTO) 1% v/v; Gel at 0.5 % v/v of Itraconazole; Optimized gel (G4) of TTO (1%) + Itz (1%). As a result of the analysis of cytotoxic potential: G4 did not show cytotoxicity during treatment being that in the first 24; concentration for 50% inhibition of the fungus in vitro (IC50) of Itz, TTO and Oilmix: respectively 40.52, 37.55 and 39.48 µg/mL; Viscosity and mucoadhesion: higher in G4. Increased gradually as vaginal pH decreased due to fungal infection; to permeation, as expected there was no cytotoxic effect. In 2006, Mondello, et. al. had already cited the main constituents of TTO, as well as Mirza, et. al (2012) who stated that Terpinen-4-ol is the main responsible for permeation (presents VO toxicity in pregnant rats); 1,8-cineol (skin irritation) and showed no effect up to 28%, present in G4 in 15%.

Nevertheless, Tobouti et al. (2014), also evaluated the joint action of TTO and Copaíba oil, respectively Melaleuca alternifolia and Copaifera officinalis, in preventing the adhesion of Candida biofilm, this biofilm is produced by the pathogen itself as a need to increase survival in an environment. They evaluated both the chemical compounds of each oil and the MIC, whose results were: M. alternifolia: 1,8-

cineole; terpinolene ɤ-terpinene, terpinen-4-ol and α-terpinene C. officinalis: trans-caryophyllene, germacrene B, α-humulene, germacrene D and α-copaene; as for the MIC of (M. alternifolia) = 0.375% (3.4 mg/ml) for ATCC10231 and 0.093% (0.84 mg/ml) for SC5314. The oil of (C. officinalis): did not inhibit C. albicans, although copaiba 10% (146.05 ± 16.15) also produced significant reduction in adhesion ($p < 0.05$). Tea tree oil, as it is popularly known, Melaleuca alternifolia oil Cheel (TTO), due to its medicinal activity, mainly antimicrobial, antiviral and antifungal, and in one of its compositions, terpinen-4-ol showed efficacy on the growth of strains of C. albicans, when resistant to conventional treatment with Fluconazole, after three weeks of infection. In studies by Haimmer et al. (2000), TTO, had both a MIC and MIC response against C. albicans of 0.25, confirming a generalized response at low concentrations; in this study, which in addition to tea tree oil contained other oils, showed susceptibility at concentrations below 0.5.

In addition, authors have proven the efficacy of TTO for several strains of Candida, analyzed in vitro, such as the study of Ergin-Arikan-Akdagli (2002) that showed proven efficacy of TTO in vaginal candidiasis mainly in cases resistant to Fluconazole, one of the main drugs used in clinical practice against Candida. The volatile oil of Santolina chamaecyparissu, also, showed potential antifungal activity as well as for vaginal and systemic candidiasis, which proves the action against several strains.

In Mondello's analyses in both 2003 and 2006 the superiority of TTO in treating resistant strains was proven. The clearance pattern of fluconazole was comparable to that induced by TTO. In terms of time there was a statistically significant difference. With TTO the infection was resolved within 3 weeks, while all other animals, untreated or treated with fluconazole, remained infected. Importantly, there was no induction of resistance to TTO.

Maruyama, et. al (2008) proved that essential oils act not only to reduce the number of viable C. albicans cells, but also to suppress neutrophil infiltration, i.e., improve vaginal inflammation.

Finally, the efficacy of the use of copaiba oil is still in need of elucidation, with studies that also explain the kinergism. This was evidenced in a study developed by Mirza, et al. (2012), by demonstrating that TTO and copaiba oil together act on recurrent Candida vulvovaginitis. In reports by Tobouti et al. (2014) attention is drawn to the study of joint action using Melaleuca alternifolia oil and Copaifera officinalis oil suggesting that, despite the inhibition of the spread of Candida by inhibiting biofilm formation, the treatment did not efficiently combat Candida infection in this association. They also report that nanoparticles are better absorbed and therefore when mixed with copaiba oil and allantoin, the diameters are smaller, which ensures better efficacy of the mixture.

Table 1. Studies evaluating in vitro the susceptibility of Candida albicans isolates to various essential oils (EOs) extracted from medicinal plants

Author / year	Type of study	Evaluation	Conclusion
Hammer KA, Carson CF, Riley TV, 1998	Susceptibility to *Malaleuca alternifolia* EO, "Tea Tree Oil" (TTO)	The Minimum Inhibitory and Fungicidal Concentrations (MIC and MFC) of TTO were the same for the various isolates incubated for 24 and 48 h, being equal to 0.25 and 0.5 %.	low concentrations (less than or equal to 0.5% v/v) and products containing tea tree oil maintained efficacy
Hammer KA, Carson CF, Riley TV, 2000	Pre and post exposure of cultures to TTO (Tea Tree Maleleuca)	Germ Tube Growth Inhibition (CTG) was observed when pre-exposed to 0.25 and 0.125% TTO, although, continued by sprouting. MIC ranged from = 0.25 to 0.5% and CFM = 0.25 to 1%.	Pre and post exposure to TTO causes widespread CTG inhibition.
Ergin, A & Arikan-Akdagli, 2002	Determine the activity of TTO against fluconazole (FLZ)-resistant isolates	The terpinen-4-ol fraction (40.8%) and the 1,8-cineol fraction (2.8%). Average MIC for TTO after 24h = 2.2% (range 0.25 to 4%), after 48h = 3% (1 to 8%).	Promising activity. May have clinical applications for the treatment of FLZ-resistant vaginal candidiasis.
D'Auria FD et al. 2005	To evaluate both *Lavandula algustifolia* Essential Oil (EO) (Lavender Oil), Linalool (97% pure) and linalyl acetate (97% pure)	CIM of Lavender EO = 0.125 to 2%, strains from vaginal infections were more susceptible than those from oropharyngeal infections (MIC respectively 0.69 and 1.04%,). CFM = 0.5 to 4% (1.1% for vaginal strains and 1.8% for oropharyngeal strains). Linalool was the most effective: MIC of 0.09% - vaginal strains and 0.29% - oropharyngeal strains; MFC of 0.1% - vaginal strains and 0.3% - oropharyngeal strains.	The oil showed effective fungistatic and fungicidal activity against dimorphism. Its activity may depend on an additive effect of its major constituents; the potential contribution of minor constituents to the antimicrobial activity cannot be excluded.
Romano, L. et al, 2005	Activity of 3 Bergamot Oils, Natural Essence (NE), Furocoumarin-Free Extract (FF) and Distillate Extract (DE)	The MIC and MFC values coincided. Overall, at 24 h readings, the MICs (for all isolates) were (v/v): NE = 5%; FF = 2.5%; DE = 1.25%; at 48 h, these values increased to 10%, 5% and 2.5%, respectively; Oil + Boric Acid combinations: Associated with 0.0235% Boric Acid .24h readings: NE = 1.25%; FF = 0.625%; DE = 0.312%; 48h readings: increased to 5%, 1.25%, and 0.625%, respectively; associated with 0.047% Boric Acid NE = 0.312%; FF = 0.312%; DE = 0.156%; 48h readings: increased to 1.25%, 0.625%, and 0.625%.	The mechanisms of antimicrobial activity of bergamot oil, as well as boric acid, are unknown. For this reason, further studies are needed to elucidate their activity against fungi and other microorganisms and to better define the therapeutic potential of these oils.
Lima I. et al., 2006	Efficacy of the EOs of Cinnamomum zeylanicum Blume (*Cinnamon*), *Citrus limon* Risso (Lemon), *Eucalyptus citriodora* HK (Eucalyptus), *Eugenia uniflora L.* (Pitanga), *Peumus boldus* Benth (Chilean Boldo) and of *Rosmarinus officinialis* L. (Rosemary).	The OEs of *E. Citriodora and R. officinalis* were tested at 8%, while *C. zeylanicum, C. limon* and *P. boldus* at 4% and *E. uniflora 2%*. Only C. *zeylanicum, C. limon and R. officinalis* inhibited *C. albicas*, with a halo of 12-13, 12 and 10 mm, respectively. The strains of *C. guilliermondii* and *C. krusei* were the most susceptible to the various EOs, while *C. tropicalis* showed the highest resistance to them.	All EOs were effective against some species of *Candida sp.* Although, *C. zeylanicum* EO showed the most outstanding results, inhibiting the growth of most strains. Consequently, there is real possibility of the application of these products in the prevention and treatment of infectious diseases of fungal origin, provided that there are more studies to prove their toxicity in vivo.

Cavalcanti et al., 2011	To evaluate the anti-adherent activity of *Rosmarinus officinalis* (rosemary) essential oil against *Candida albicans*. Focusing on oral candidiasis.	In this concentration, at 0h there was disorganization of the cell matrix, rupture of the cell wall and denaturation of structures. At this concentration, at 0h there was disorganization of the matrix, rupture of the cell wall and denaturation of structures. And in 24h the cells were atrophied, with an intact wall, but the inhibition of adhesion was greater. In the concentration of 2.25 mg/mL there was significant inhibition of adhesion and cellular rupture from 0 to 24 h.	The EO of *R. officinalis* caused changes in both morphology and adherence of *C. albicans*.
Castro, R.D.; Lima, E.O. 2011	To evaluate, in vitro, the EOs of *Ocotea odorifera* Vell. (sassafras) and *Rosmarinus officinalis* L. (rosemary).	MIC: Sassafras oil = 2.5 mg/mL on 68% of strains. Rosemary oil = 5 mg/mL on 81% of strains.	*Candida* sp. strains showed resistance to sassafras and rosemary EOs, possessing weak activity on fungal species involved in oral cavity infections.
Castro, R.D., Lima, E.O, 2012	In vitro evaluation of the EOs of Citrus reticulata (Clove Tangerine); Citrus aurantifolia (Tahiti Lemon); Cinnamomum zeylanicum (Cinnamon); Matricaria chamomilla (Blue Chamomile); Mentha piperita (Peppermint); Eugenia uniflora (Pitanga) and Zingiber officinale (Ginger) on Candida strains involved in oral cavity infections.	Diameter of the inhibition zone caused by Cinnamon, Lemon and Mint were 48, 30 and 19 mm, respectively. The only MIC measured was for cinnamon (312 µg/mL.), which showed the best antifungal effect.	Only Cinnamon and Lemon EOs inhibited 100% of the isolates. Although all the EOs showed antifungal potential. *C. zeylanicum* and *C. aurantifolia*, represent possible agents in the prevention and treatment of infectious diseases of fungal origin, including oral candidosis.
Carvalhinho et al, 2012	To analyze the susceptibility and efficacy in isolates of patients with orthodontic appliances to mouth rinses, antifungal agents and OEs from Lemon (*Citrus limonum* L.), Eucalyptus (*Myrtaceae, Eucalyptus)*, Myrrh (*Commiphora myrrha (*Nees) Engl.), Cinnamon (*Cinnamomum zeylanicum* Blume), Laurel (Laurus nobilis L.), Mint (*Mentha piperita L.), Rosemary* (*Rosmarinus officinalis* L.) and	For susceptibility testing, 15µL of each essential oil were placed on virgin discs (6 mm diameter), allowed to dry and placed on MH plate, previously inoculated with 0.5 McFarland yeast suspension. The plates were incubated at 36 ± 1C for 24-48 h, and dz (mm) read.	Based on the average dz, the essential oil activities followed the profile cinnamon > bay > mint > eucalyptus > rosemary > lemon > myrrh > mandarin. EO extracts demonstrated antifungal activity to a lesser degree than antifungal agents and mouthrinses. The use of EOs such as cinnamon, bay leaves, and mint may be a viable alternative, alone or in combination with antifungal agents, for therapeutic and/or preventive purposes against oral candidosis caused by the use of orthodontic devices.

	Tangerine (*Citrus reticulata* Blanco).		
Cavalcanti et al, 2012	Antifungal activity of the EOs of pear orange (*Citrus aurantium*), Sicilian lemon (Citrus *limmom),* carnation mandarin (Citrus *reticulata)*, guabiroba (*Campomanesia xanthocarpa)* pindaíba (*Xylopia brasiliensis)*, basil (Ocimum basilicum) and Brazilian palmarosa (Cymbopogon martinii).	The OEs of *O. basilicum* and *C. martinii* inhibited the isolates at concentrations below 100 mg/mL.	All tested products showed antifungal activity, evidenced by inhibition diameter > 8 mm. The EOs of *C. martinii*, *O. basilicum and C. xanthocarpa* had the highest efficacy against the isolates, inhibition halos of 40, 30 and 20 mm, respectively.
Cleff et al, 2012	To identify the major chemical constituents using gas chromatography in rosemary essential oil and evaluate the antifungal properties in isolates from the microbiota and from clinical cases of candidiasis in animals.	Main compounds: Camphor (~56.00%), 1,8-cineol (~16.00%), verbenone (~7.80%) and myrcene (~4.00%), α-terpineol (~3.70%), borneol and linalool (~2.00%), p-cymene (1.50%), 4-terpineol (1.39%). Variation of MIC and CFM against *C. albicans* 1.25 to 2.5 µL/mL and 2.5 to 5.0 µL/mL; Against animal isolates was MIC = 2.5 to >10.0 µL/mL and CFM = 5.0 to >10.0 µL/mL.	Rosemary EO showed fungicidal and fungistatic activity in vitro.
Brito et al, 2015	To evaluate the antifungal activity, in vitro, of the EO of rosemary pepper (*Lippia sidoides* Cham.) and its major compound, Thymol	MIC and CFM (µg/mL) *L. sidoides* = 64 - 256 and 128 - 512 , Thymol = 32 - 64 and 64 - 128. *C. krusei* and *C. tropicalis* strains showed changes in their dimorphic potential when exposed to *L. sidoides* EO with absence of hyphae and pseudo hyphae. The inhibition effect was directly proportional to the concentration. But, it did not interfere in the morphologic transition of *C. albicans*. Thymol interfered in the morphology of *C. albicans*, with alterations in all concentrations, absence of hyphae or pseudohyphae, without influencing *C. krusei.*	Rosemary pepper EO and its compound thymol showed expressive anti-fungal potential with relevance for all strains, even causing fungicidal effect. They caused morphological alterations in the fungal cells, inhibiting or reducing the emission of hyphae and pseudohyphae. Further studies will be necessary to investigate the mechanism of action.
Minooeianhaghighi MH, Sepehrian L, Shokri H. 2017	To determine the chemical compounds and *in vitro* antifungal susceptibility of the essential oils and their combinations of *Cuminum cymunim* (cumin) and *Lavandula binaludensis* (lavender) against strains isolated from patients with recurrent vulvovaginal candidiasis (CVVR).	Components of C. cyminum: terpinene (21.07%); cuminaldehyde (18.80%); 2-norpinene-2-carboxaldehyde (16.68%); L. binaludensis: 1,8-cineol (71.56%); cyclopentapyron (4.72%); O-cymene (4.05%) Average MIC of Cumin and Lavender: 8.00±1.89 vs. 7.91±1.61 µg/mL Mean CFM: 15.82±3.22 vs. 16.20±5.11 µg/mL. The highest percentages of inhibitory concentration were 80% and 70% at	It is concluded that *C. cyminum* and *L. binaludensis* essential oils have good antifungal activity. The CVVR isolates showed lower susceptibility to the cumin oil MIC than the lavender oil. The coupling of oils also showed similar inhibitory effect.

	The study was approved by the Iranian Ministry of Health and all women gave consent.	the concentration of 7.81 µg/mL, respectively. The combination of the two EOs showed the same activity when compared to each oil, with similar MIC (mean: 7.22±1.69 µg/mL) and MFC (mean: 14.84±3.26 µg/mL).	
Vieira et al., 2019	In vitro analysis of the essential oils of *Cuminum cyminum* (cumin), *Anethum graveolens (*dill), *Pimpinella anisum* (anise) and *Foeniculum vulgare* (fennel/sweet herb).	CIM of cumin EO = 2.188 to 4.375 mg/mL; CIM of fennel EO = 4.375 to 8.75 mg/mL; CIM of anise and dill = 8.75 mg/mL.	All isolates showed susceptibility to the evaluated EOs. C. cyminum exhibited the lowest MIC. The cumin, anise and fennel EOs were not cytotoxic to mouse fibroblasts at the same MICs found for the tested yeasts. However, dill oil at concentrations of 20 and 8 mg/mL was.

Table 2. In vivo studies showing the effects of Essential Oils (EO) against Candida albicans infections

Author / year	Type of study	Evaluation	Conclusion
Suresh et al, 1997	Analysis of the effectiveness of *Santolina chamaecyparissus* oil	OE CIM. Treatment via vaginal (with swabbing), oral, and hair root.	Effective treatment, has antifungal potential.
Mondello et al, 2003	In vitro and in vivo evaluation of Melaleuca alternifolia oil (TTO)	Administration of TTO intravaginally (0.1 mL at 1%, 2.5% and 5%, in 0.001% Tween-80), 1, 24 and 48 h after intravaginal infection. Infection was monitored for at least 21 days after inoculation, with vaginal secretion being collected usually at 1, 24 and 48 h, then at days 5, 7, 14 and 21	Effective treatment with both fluconazole-susceptible and fluconazole-resistant isolates.
Chami et al, 2004	Analysis of Carvacrol and Eugenol (respective components of the OEs of Oregano and Clove).	In vitro MICs of C and E were 103 mg/L, 2x103 mg/L, and 5.44 mg/L, respectively. 500 µL, 2x a day, intravaginally, of C or E to a final concentration of 2 x 103 mg / L (±10 mg / kg / day), 4 x 103 mg / L, (±20 mg / kg / day), respectively. Prophylaxis: start doses 2 days before inoculation until 3 days after. Therapeutic: start 72 hours after inoculation until day 7.	They are promising for the treatment and prevention of vaginal candidiasis, especially for prophylaxis in AIDS patients.
Mondello et al., 2006	Investigate, in vitro and in vivo, two critical bioactive constituents of TTO, terpinen-4-ol and 1,8-cineole.	In vitro activity: Terpinen-4-ol and 1,8-cineole inhibited all the isolates tested. MICs and MFCs ranged for: terpinen-4-ol = 0.015% to 0.06%; 1,8-cineol = 1% to > 4% v/v; TTO = 0.06% to 0.5% v/v In vivo activity: Cineol did not participate because it has weak antifungal action. Administration via intravaginal route 1, 24 and 48h after inoculation (TTO - 0.1 mL at 1%, 2.5% and 5%; terpinen-4-ol 0.1 mL at 1% for). Infection was monitored with vaginal fluid sampling being done at 1, 24 and 48 hours, then on days 5, 7, 14 and 21.	As with all dosing regimens, the infection was cleared within 3 weeks. Identification of terpinen-4-ol as a single active constituent in vivo of the TTO mixture. Highlighting the therapeutic potential of this purified constituent, thus avoiding the need for laborious and costly quality control of a mixture of compounds. There remains a clear need for preclinical and clinical investigations aimed at a broader evaluation of terpinen-4-ol, including studies on the mechanisms of anticandidal activity.
Maruyama et al., 2008	To investigate, in vivo, the effectiveness of active administration methods of Essential Oils (EOs), especially Geranium Oil,	On day 1 to 3, 10 µL (25 µg/mL concentration of essential oils suspended in solution were injected vaginally. Administration of 10 µL of 5 and 1% Geranium and Tea Tree Oils, and doses of 0.2	Vaginal applications of the oils can be effective in treating candidiasis when combined with vaginal washing. The in vitro study showed that a very low concentration (25 µg/mL) of the oils

	along with their effect against *Candida albicans* growth.	and 1.0% of Oregano, Lemongrass and Clove Essential Oils had no influence on CFU. Vaginal washing was done once a day for 3 days and CFU was measured on the 4th. This reduced the number of viable *C. albicans* cells compared to the control without washing. The combination treatments between the EOs and washing were started 2 days after Candida inoculation. The oils were applied vaginally immediately after washing (0 h) and 3 h after. CFU was measured at the time of the first wash (0 h) and 6, 24 and 96 h after the first oil application. The relative value of each hour was compared with 0 h. In vitro: Inhibitory concentration of geranium EO, in the range of 25 and 50 µg/mL decreased the number of mycelial forms, but not yeasts. Above 100 µg/mL it inhibited the yeasts in a dose dependent way. The same did not occur with geraniol, despite keeping these same concentrations.	inhibited mycelial growth, but not yeast growth. The EOs are ineffective when used alone, without vaginal washing. In the control group washing alone, CFU reached a maximum in 24 h and maintained this level for 96 h. On the other hand, geranium and geraniol oils decreased the number of cells 6 h after the first application, and the effect of each was increased in a time-dependent manner. The relative CFU at 96 h decreased to 1/10 compared to the control.
Pietrella et al, 2011	In vitro and in vivo testing of *Mentha suaveolens* EO (EOMS), using jasmine oil (JO) (*Jasminum grandiflorum*) as a negative control and tea tree oil (TTO) as a positive control.	Respective MIC and MFC values: EOMS= 0.39-0.78 g/L and 0.39-1.56 g/L TTO = 0.78 - 3.12 g/L and 1.56-6.24 g/L. Yeast and hyphae inhibitory effect: EOMS = 0.05 and 0.098 g/L TTO = 0.098 and 0.39 g/L. JO did not affect the growth of any strain. Intravaginal treatment with the OEs (500 µg / 10 µl / mouse) was started 2 h before the first inoculation and then was repeated every 2 days until the 21st. Fungal load in the vagina was quantified as photon emission and also CFU of the fluids.	TTO was less efficient than EOMS, especially when the oils were tested against fluconazole-resistant strains. At a concentration of 2 × MIC (0.78 g / L), the number of colonies was significantly reduced after 24 hours of incubation and the full fungicidal effect was observed within 48 hours of contact. EOMS in vivo accelerates the clearance of *C. albicans* during vaginal infection. In this model, and under the conditions tested, TTO was only minimally effective in causing a significant reduction in vaginal fungal burden, measured as photon emission at 9 and 15 days. No effect was recorded after 21 days of infection.
Trinh, et al., 2011	To investigate the inhibitory effects of *Artemisia princeps* Pamp Essential Oil (APEO) and its major constituents examined in vitro and in vivo.	APEO was subjected to GC/MS. Main compounds: eucalyptol (21.1%), borneol (12.2%), 4-terpineol (8.7%), α-terpineol (8.2%), camphor (6.2%) and others. Determination of MICs and CFMs (%v/v): APEO = 0.25 and 0.5 α-terpineol = 0.125 and 0.25 eucalyptol = 1 and > 1. Starting on day 1 post-infection, α-terpineol, eucalyptol and APEO (10% v/v) were prepared and administered vaginally, 1 time/day for 3 days at 20 µL/camundongo	Topical treatment with APEO, eucalyptol or α-terpineol significantly reduced the viable counts of C. albicans with α-terpineol standing out, which showed less MIC and CFM.
Li et al., 2012	Investigation of the in vitro activity of Pogostone (PO), an EO extracted from *Pogostemon cablin*, and its efficacy in the treatment of fluconazole-resistant *C. albicans* vaginitis (FLC).	MIC = 3.13 - 100 µg/ml (25 µg/ml was the mode); CFM = 50 - 400 µg/ml. Vaginal swabs were obtained on days 3, 5, 7, 11 and 15 after infection to estimate Candida load. PO was applied intravaginally once daily at 1, 2 and 4 mg/kg body weight at concentrations of 80, 160 and 320 times the MIC. In addition, it was administered once daily at 20, 40 and 80 mg/kg body weight by oral gavage post-infection. Mean Lethal Dose (LD50) PO: LD_{50} PO = 355 mg/kg	The efficacy of both in vitro tests and in an animal model indicate the potential of OP in the treatment of *Candida* sp infections.
Mirza et al., 2012.	Production of a thermosensitive, stable gel based on Tea Tree Oil (TTO), Itraconazole (Itz), and its synergistic effect in combating recurrent vulvovaginal candidiasis (CVVR) in winstar rats.	Gel of TTO 1% v/v; Gel at 0.5 % v/v of Itz; Optimized gel (G4) = TTO (1%) + Itz (1%). IC50 of Itz, TTO and Oilmix obtained after a 48 h study was 40.52; 37.55 and 39.48 µg/mL, respectively. Mice were treated once daily with 0.5 g gel (G4) for 14 days. Before each administration, the rats were evaluated	The synergism of the thermosensitive gel was effective in treating CVVR; The authors conclude that it can be exploited in clinical applications.

		for vaginal or vulvar irritation, secretion or bleeding from the vagina.	
SANTOS et al., 2017.	To evaluate the efficacy of *Punica granatum* Linn (pomegranate) gel in preventing oral candidiasis in patients undergoing radiotherapy with or without chemotherapy for head and neck squamous cell carcinoma, and adverse effects associated with its use	Group 1 (n=11) used the prophylactic gel 6.25%, since the beginning of radiotherapy, associated or not with chemotherapy and concluded one week after the end of it with frequency of 4x/day, 30 min after oral hygiene. Group 2 (n = 6) used Miconazole gel 2%, as prevention following the same protocol as the previous group. The patients were evaluated weekly during the whole antineoplastic treatment. They were submitted to culture tests if they presented clinical signs/symptoms of fungal infection. In case of a positive result for *Candida*, they stopped participating in the research and introduced the treatment protocol for oral candidiasis.	The gel proved effective against oral candidiasis, which was absent in 63.6% of G1 patients and in all G2 patients. In addition there was no association of adverse effects.

Table 3. Studies on Copaifera sp. oil (Copaíba) from Brazilian biodiversity against Candida albicans isolates.

Author / year	**Type of study**	**Evaluation**	**Conclusion**
God et al, 2011	In vitro evaluation of the Resin Oil (OR) and Essential Oil (EO) from *Copaifera multijuga* Hayne, comparing its fungitoxicity with Miconazole Nitrate (NM)	Halo of Inhibition (mm): OR: 7.0 - 9.0 OE: 9.5 - 16.0 NM: 10.0 - 15.0 MIC (mg/mL) (OR) = 0.3 - 0.6 (OE) = 0.1 - 0.5 (NM) = 0.1 - 0.5	Indices equal to or greater than 85% present a good potential for antimicrobial action for practical uses, which is why we can say that the essential oil of *Copaifera multijuga* Hayne may be a good indication for more specific studies on combating candidiasis.
Lima et al, 2011	Reproductive trials, at the pre-clinical level, in animals treated with vaginal cream containing resin oil from *Copaifera duckei* Dwyer.	Treatment of pregnant rats: Control Group (CG): Only 0.5 ml of vaginal saline for 30 days throughout pregnancy; Treated Group with Base Vaginal Cream (TBVC): Only the base vaginal cream, via vaginal route, in the same amount as the group treated with copaiba vaginal cream, for 30 days and throughout gestation; Group Treated with Copaiba Vaginal Cream (TCVC): A dose of 28.6 mg/kg of copaiba vaginal cream, vaginally, corresponding to 10x the dose that would be used in humans, for 30 d and throughout pregnancy	Treatment with the vaginal cream containing copaiba resin oil did not affect maternal weight at any stage of pregnancy. Thus, it did not interfere with reproductive performance during pregnancy at the dose tested. In addition, there were no external anomalies or fetal malformations. Therefore, the vaginal cream with 2.5% copaiba oil was shown to be safe during pregnancy in Wistar rats (*Rattus norvegicus*).
Tobouti et al., 2014	To evaluate the effectiveness in inhibiting biofilm adhesion of *Candida albicans* by the EO of *Melaleuca alternifolia* and *Copaifera officinalis*.	MIC (M. alternifolia) = 0.375% (3.4 mg/ml) and 0.093% (0.84 mg/ml) CIM (C. officinalis): Not obtained.	*C. officinalis* oil): did not inhibit *C. albicans*, although 10% copaiba (146.05 ± 16.15) also produced significant reduction in adhesion ($p < 0.05$) *C. officinalis* and *M. alternifolia* oils have inhibitory effect on *Candida albicans* adhesion and suggest the prophylactic use of these oils against candidiasis.
LIMA et al., 2017	Based on the application of vaginal cream of *Copaifera duckei* Dwyer resin oil (ORC), this study aimed to evaluate the toxic effects of the subchronic treatment phase.	Treatment was 7 days and for subacute treatment phase toxicity (22 days), orally (p.o), by gavage and intravaginally (ivag). The groups received doses of 0.04 mg/kg, 28 mg/kg and 32 mg/kg, respectively, with ORC (p.o), ORCV (ivag) and CVC (ivag). Experimental groups: Orally treated with *C. duckei* oil-resin and distilled water (ORC and Control). Intravaginal treatment with C. duckei oil-resin vaginal cream (CVC), *C. duckei* oil-resin only (ORCV) and the control group, with the basic vaginal cream (CVC control).	Subacute treatment with copaiba oil-resin (orally and intravaginally) and *C. duckei* cream (CVC) was effective, caused no clinical signs of toxicity, no deaths were reported, and did not significantly alter the parameters evaluated in this study.

Technological perspectives applied to clinical trials and biomedicine interests

In Brazil, it is recurrent to mention the necessary application of new technologies applied to support research, especially involving epidemiological and clinical data, in order to substantiate decision-making in terms of public health policies. In biomedicine, including perspectives of microbiological assays and clinical tests with essential oils, as in the case of the present study, there are still gaps in the development of studies carried out, where the use of digital technology is certainly an increasingly urgent need due to the relevance of agility in research protocols, methodological procedures and analysis of their results, if it is pertinent to the type of study idealized by researchers. However, this part still requires greater speed in Brazil, given its importance and the possible dynamism to implement, from the ordering of the data to its analysis with the rigorous criteria inherent to science. According to the Association of American Medical Colleges Task Force on Clinical Research, clinical research is defined as research in health care aimed at producing knowledge essential to the understanding of the mechanisms, prevention, and treatment of diseases, as well as health promotion, Just as the European Agency has already highlighted that for the Evaluation of Medicinal Products, clinical research is an "investigation in human beings, with the purpose of discovering or verifying the pharmacodynamic, pharmacological, clinical and/or other effects of the product(s) and/or identifying adverse reactions to the product(s) under investigation, and must meet the objective of ascertaining its safety and/or efficacy" (BRASIL, 2011). There is already a framework of institutional frameworks that strengthen, guide and encourage the activities of Research and Development (R&D) in the country and that clinical research generates scientific knowledge for the resolution of public health problems, from subsidies aimed at the generation of new technologies or improvement of existing techniques, processes and technologies, which, in turn, will be produced, marketed and used in its different segments.(Tenório et al., 2017). However, in Brazil, although there is already interaction between the National Innovation Systems (NIS) and technologies being used, there are still many gaps concerning the planning and delineations of scientific studies using artificial intelligence, for example. In the global agenda of scientific research in health, it is important to strengthen the technological and innovation aspects, even the internationalization of clinical trials, which would create new structures of innovation in health and new opportunities for the international dissemination of knowledge and production, as emphasized by Oliveira and Viana (2019).

Among some technologies applied in clinical research, there are Artificial Intelligence as an innovation in data analysis, anchoring the design of clinical trials and assisting in the clear association of hypotheses to results and minimize risks and/or potential biases of the analysis, still with broad utility in the recruitment of participants for clinical research using electronic health records and data from connected devices to match patients with tests and allow large-scale mining and advanced analysis of a large amount of data generated from many different digital sources in virtual tests, besides the advantage also of tracking; also highlights the use mHealth Wearable, as devices can be watch; smartphones, tablets and mobile

applications in order to compose virtual testing technology tool and interactive design, which can ensure the individuality of the participant among several other aspects linked to ethics and regulation of clinical research involving humans, where this technology may be able to support the value chain of clinical research, such as recruitment and enrollment of patients, terms of free and informed consent, data collection and registration in connected devices, communication and patient engagement, with customizable and compatible applications for the research participant as well as the researcher, which contributes to agile, easy, convenient, continuous and safe participation, besides facilities such as telemedicine visits with investigators, in case foreseen in the methodology and approved by the regulatory instances.

Thus, it is necessary to strengthen learning in the areas of technology and innovation in health in Brazil, certainly already existing but with an increasingly urgent need for institutionalization in universities, which can be in undergraduate and graduate courses, for example in health courses such as medicine and pharmacy as well as those related to technology and engineering, such as biomedical engineering and related to these areas of knowledge. It is necessary to advance in the implementation of public policies to promote research, as well as from private incentives, both still incipient for innovation and technology applied to the processes of clinical research, especially.

4 CONCLUSION

Evidence points to the use of essential oils, among them, copaiba oil as an alternative for potential phytotherapeutic drugs in Brazil, since they present satisfactory antimicrobial action against the organism C. albicans and with absence and/or low toxicity under certain conditions, being a relevant indicator for clinical trials. In the public health context, especially, it is understood as relevant to count on this alternative in complementary health medicine and thus minimize problems arising from possible resistance and/or toxicity to drugs from the azole group, in adverse circumstances, and even through the costs of the medicine. The clinical application of essential oils represents a necessary advance in research and for human health, being prospected in recent studies in the world and in Brazil. Brazil is one of the largest producers of essential oils and has in its megabiodiversity an alternative of institutional, social, environmental and economic development, considering the necessary and current perspective of strengthening the sustainability agenda.

As for efficacy, specifically regarding copaiba oil, both the Essential Oil and Resin Oil showed good antimicrobial activity against fungi of the candida genus, with rates equal to or greater than 85% efficacy. As for the form of presentation of possible phytotherapic derived from copaiba oil, the recommendation for the vaginal oil compound (2.5%) of Copaifera multijuga Hayne stands out, being safe to use during pregnancy when tested in pregnant rats, as well as showing no toxicity in subclinical treatment.

It is important to verify in further studies the effect of the association between essential oils, because it was identified effective synergism between TTO and copaiba oil, potentiating the effect in the treatment

of vulvovaginitis of repetition. Also, the phytochemical constituent terpinen-4-ol was highlighted as a single active constituent in vivo of the TTO mixture. Nanoencapsulation improved the antifungal activity of copaiba oil, which was enhanced by the presence of allantoin. Thus, such aspects should be further explored in clinical applications.

Although Copaifera officinalis does not completely inhibit C. albicans, it may reduce biofilm adhesion, so these authors suggest the prophylactic use of these oils against candidiasis. Few studies have proven dual efficacy against candidiasis and vaginosis (G. vaginalis and C. albicans), however some oils being Mugwort and Geranium oils showed dual therapeutic action, due to their basic constituents: α-terpineol, inhibit bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) by inhibiting the growth of vaginal pathogens and activating NF-κB. and geraniol respectively. The main candida strains used in the studies were C. albicans and C. krusei.whereas the Copaiba species were Copaifera multijuga Hayne, Copaifera duckei, and Copaifera officinalis.

Among the limiting factors of the study is the lack of clear determination of the framework by the authors reviewed regarding the quality of the studies included. However, this fact was minimized since the search was prioritized by accessing scientific journals of minimum impact qualis B capes, peer-reviewed, with editorial board, with D.O.I and indexing platforms validated in the scientific academic environment both nationally and in international journals with content open for free consultation. Another fact concerns the lack of studies that reported the statistical analysis of the data, being a gap in the studies carried out. The research bias was minimized by involving two authors among the others, for search purposes and to meet the eligibility criteria of the studies.

However, it is believed that the present study constitutes a basis for future clinical research, since it was possible to highlight some relevant points, namely: it is confirmed that copaiba oil showed a satisfactory antimicrobial action against the most studied standard pathogen, which was C. albicans, despite the few studies especially regarding the dose and the mixture, as well as the absence of clearer elucidation regarding the action of some isolated constituents; there are indications of effective and safe use and non-toxicity of the resin oil, suggesting safety in the use through the intravaginal route, which opens up prospects for continuing the studies also in this area, given the relevance of incorporating complementary alternative practices in primary health care, especially in SUS. This is a research action that is in line with the National Policy on Medicinal Plants and Herbal Medicines, which requires innovation of products and/or processes from potential medicinal plant species and has prospects for application through the current scenario: Brazil is one of the world's largest producers of essential oils, including copaiba oil, and has in its megabiodiversity an alternative institutional, social, environmental and economic development, given the necessary and current perspective of strengthening the sustainability agenda.

Another aspect to be highlighted in this study is that in Brazil it is improved and/or implemented through strengthened learning in technological and innovation areas in health. There is an urgent need for

more and more institutionalization in universities, which can be in undergraduate and graduate courses, such as medicine and pharmacy, as well as courses related to technologies and engineering, such as biomedical engineering and related to these areas of knowledge. Notably, for this to occur, it is important that concomitantly the implementation of public policies for the promotion of research can be strengthened, as well as those coming from private incentives, because both are still very incipient for innovation and technology applied to clinical research processes, especially.

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