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Copaiba oil as a natural product challenge in the chemistry, pharmacological and biotecnological fields

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Outline

Introduction

Copaiba oil is obtained from trees of the *Copaifera* genus and became an important medicinal source particularly concerning to Amazonian region of Brazil wherein since the 16th century has been largely used in Brazilian folk medicine. Among the 106 predict species of the genus *Copaifera* (Leguminosae), only 49 have been validated and the remaining species are unresolved. Particularly in Brazil 17 species can be found but there are only 9 main species, such as: *C. duckei* Dwyer*, C. glycycarpa* Ducke*, C. guyanensis* Desf.*, C. martti* Hayne*, C. multijuga* Hayne*, C. paupera* Herzog, *C. piresii* Ducke*, C. publiflora* Benth, and *C. reticulata* Ducke. Among them the greatest natural sources of copaiba oil are *C. reticulate* (70% of oil production), *C. multijuga* (10%) and *C. guianensis* (10%) (ARRUDA et al., 2019; LEANDRO et al., 2012; VEIGA JÚNIOR; PINTO, 2002).

Copaiba oil is a transparent liquid ranging from yellow to light brown color, and is excreted as a plant defense against animals, fungi and bacteria. Its production could occasionally produce 30 L/tree in a single collection but the lower amounts (0.3 to 4 L/tree) are usually expected. In this sense, copaiba oil extraction for the specimens *C. officinalis* Jacq. L. and *C. reticulate*, seems optimal for dry season harvest. Meanwhile, from *C. venezuelana* and *C. pubiflora* Benth this oil yield may peak with a great fluidity, in the rainy season (ALMEIDA et al., 2012; PAIVA et al., 2002, SANDNA et al., 2018; VEIGA JÚNIOR et al., 1997; VEIGA JÚNIOR; PINTO, 2002).

Generally, copaiba oleoresin is largely used in cosmetics and perfume industries as an important raw material as fixer, with fresh and acres notes which are compatible with traditional floral products. Along with its emollient property, this oil shows additional benefits such as antibacterial and anti-inflammatory therapeutics on manufacture soaps, creams and bath foams. Aiming at to soften hair, shampoos, conditioners, creams, lotions and capillaries, copaiba oil have also been largely commercialized (ALMEIDA et al., 2012; DEL NUNZIO, 1985; MACIEL et al., 2002; VEIGA JÚNIOR et al., 2005). Among other uses, copaiba oil act as a protective agent applied on metal surfaces (EMERENCIANO et al., 2017), as drying product in the varnish industry replacing the use of linseed oil (ALBUQUERQUE et al., 2017; ARRUDA et al., 2019; DIEFENBACH et al., 2018; FERRO et al., 2018; TOBOUTI et al., 2017).

The present updating of copaiba oil brings a compilation data focusing on its ongoing biotechnological advances and point towards the safe bioavailability of this important natural product, which is herein discussed along with its foremost importance on phytochemical and medicinal properties. Also, point out its therapeutic potential on wound healing and highlight in a general vision the drug delivery field progress in nanomedicine. Finally, associate the challenges of copaiba oil as a traditional floral product in the transition of nanomedicine products into the modern commercial products and beyond.

Material and Methods

The searched literature for this review was collected from different scientific sources such as Web of Science, PubMed, Google Scholar, and the brazilian virtual library CAPES´ Periodics Portal which includes ScienceDirect and others scientific resources. Phytochemical and pharmacological studies published for copaiba oil, in English or Portuguese, were taken in account and also expanded to the progress of copaiba oil in nanomedicine on the therapeutic potencial of natural products and its dominant market.

Results

Phytochemical and medicinal properties of copaiba oil

The chemical composition, color, and viscosity of copaiba oil vary according to each species and regions, but usually are complex mixtures of chemicals. Because of that, copaiba oil become a huge challenge to the chemist of natural products and pharmacologist researchers. According to previously reports of copaiba oleoresin composition, there are described 72 sesquiterpenes and 28 diterpenes. However, only a few species of *Copaifera* have a full studied chemical composition wherein both oleoresin and volatile fractions were analyzed. Table 9.1 to 9.6 shows for some *Copaiferas species* their major components identified in their copaiba oil samples by applying phytochemical studies, as well as the plant natural occurrence and the country of the developed study. Among them *C. multijuga* Hayne is the most studied species, followed by *C. reticulata* Ducke, *C. langsdorffii* Desf., *C. officinalis* (Jacq.) L., *C. cearensis* Huber ex Ducke, *C. guianensis* Desf., *C. lucens* Dwyer, *C. martii* Hayne, *C. paupera* (Herzog) Dwyer, *C. piresii* Ducke, *C. publiflora* Benth, and *C. trapezifolia* Hayne. By comparing the results data, it is well known that te presence and concentration of copaiba oil components often shows conflicting data. Despite this chemical variation the substances detected are basically the same, with different concentrations, but it still controversial that extraction according to day hour cause significant variations (ARRUDA et al., 2019; MACIEL et al., 2002; SANDNA et al., 2018; VEIGA JÚNIOR; PINTO, 2002).

From the phytochemical studies it was realized that chromatography modifications procedures improve isolation and purification of the bioactive copaiba oil constituents. In this sense, some examples are described forward for some copaiba oil which were characterized by GC/MS. The findings confirmed the occurrence of sesquiterpenes volatile compounds such as: β-caryophyllene, caryophyllene oxide, α-copaene, α-humulene, τ-muurolene, β-bisabolene and β-bisabolol. But the sesquiterpene β-caryophyllene is usually the major constituent of *Copaifera* specimens and become the most used biomarker to authenticate copaiba oilsamples (VEIGA JÚNIOR et al., 1997; VEIGA JÚNIOR; PINTO, 2002).

TABLE 9.1
Copaifera multijuga Hayne species occurrence and major components.

Major Components	Country Occurrence	Reference and Country Study
β-caryophyllene (5.1-64.0%) α-copaene (2.0-15.0%) copalic acid (1.7-7.1%) caryophyllene oxide (0.2-31.5%) α-humulene (0-8.9%) germacrene D (0-16.7%) δ-cadinene (0–5.4%)	Brazil	SOUZA-BARBOSA et al., 2012 (Brazil)
β-caryophyllene (10.6-62.7%) α-copaene (2.5-14.9%) α-humulene (2.4-8.7%) copalic acid (1.1-5.2%)	Brazil	SOUZA-BARBOSA et al., 2013 (Brazil)

germacrene D (0-18.9%) caryophyllene oxide (0.2-32.5%)		
β-caryophyllene (42.9-60.3%) *trans*-β-bergamotene (2.0-7.0%) caryophyllene oxide (tr-8.8%) α-copaene (2.1-5.2%) copalic acid (1.9-11.0%) 3-acetoxycopalic acid (0.8-6.2%)	Brazil	CASCON; GILBERT, 2000 (Brazil)
β-caryophyllene (60.2%) copalic acid (9.5%) α-humulene (8.6%) *trans*-α-bergamotene (6.4%)	Brazil	SANT'ANNA et al., 2007 (Brazil)
β-caryophyllene (57.5%) α-humulene (8.3%) copalic acid (6.2%)	Brazil	VEIGA JUNIOR et al., 2007 (Brazil)
β-caryophyllene (57.5%) copalic acid (6.2%)	Brazil	SANTOS et al., 2008 (Brazil)
β-caryophyllene (57.5%) α-humulene (8.3%) copalic acid (6.2%)	Brazil	LIMA et al., 2003 (Brazil)
β-caryophyllene (57.1%) α-humulene (10.2%) β-sesquiphellandrene (9.9%)	Brazil	TRINDADE et al., 2013 (Brazil)
β-caryophyllene (36.0%) α-copaene (18.8%) β-bisabolene (8.5%) *trans*-α-bergamotene (7.0%) δ-cadinene (6.1%)	Brazil	KOBAYASHI et al., 2011 (Brazil)

Tr = traces.
Source: by author

TABLE 9.2
Copaifera reticulata Ducke species occurrence and major components.

Major Components	Country Occurrence	Country Study and Reference
β-caryophyllene (1.4-68.0%) *trans*-α-bergamotene (2.4-29.6%) β-bisabolene (3.7-42.4%) caryophyllene oxide (0.1-15.2%) β-elemene (0.5-5.6%) α-humulene (1.1-9.7%) β-selinene (0-20.6%)	Brazil	ZOGHBI et al., 2009 (Brazil)

α-selinene (0-13.2%)		
β-caryophyllene (25.1-50.2%) *trans*-α-bergamotene (6.4-12.0%) β-bisabolene (5.2-17.4%) α-humulene (4.1-5.8%) β-selinene (1.8-6.7%)	Brazil	SACHETTI et al., 2011 (Brazil)
β-caryophyllene (0-43.4%) *trans*-α-bergamotene (12.0-32.8%) β-bisabolene (24.2-50.3%) β-elemene (0-6.0%) α-guaiene (0-9.5%) *trans*-β-guaiene (0-5.8%) α-humulene (0-7.0%) β-selinene (0-17.1%) α-selinene (0-10.4%)	Brazil	HERRERO-JÁUREGUI et al., 2011 (Spain)*****
β-caryophyllene (40.9%) α-humulene (6.0%) germacrene D (5.0%)	Brazil	VEIGA JUNIOR et al., 2007 (Brazil)
β-caryophyllene (37.3%) *trans*-α-bergamotene (9.0%) β-bisabolene (14.5%) α-humulene + (E)-β-farnesene (5.4%)	Brazil	TEIXEIRA et al., 2017 (Brazil)
β-caryophyllene (37.3%) *trans*-α-bergamotene (9.0%) β-bisabolene (14.5%) α-humulene (5.4%)	Brazil	GUIMARÃES-SANTOS et al., 2012 (Brazil)
β-caryophyllene (7.7%) *trans*-α-bergamotene (22.0%) β-bisabolene (24.9%) β-selinene (12.2%) α-selinene (11.4%)	Brazil	BARDAJÍ et al., 2016. (Brazil)

*****copaiba oil collected from Brazil.
Source: by author

TABLE 9.3
Copaifera langsdorffii Desf. species occurence and major components.

Major Components	**Major* Country Occurrence**	**Reference and Country Study**
β-caryophyllene (5.5%) *trans*-α-bergamotene (48.4%) cyclosativene (5.0%) β-elemene (5.1%)	Brazil	GELMINI et al., 2013 (Italy)**

α-himachalene (11.2%) β-selinene (5.0%)		
β-caryophyllene (32.8%) copalic acid (5.6%) hardwickiic acid (8.2%) kaurenoic acid (44.3%)	Brazil	SANTOS et al., 2008 (Brazil)
β-caryophyllene (31.4%) eremophilone (6.8%) kaurene (6.8%) methyl oleate (26.5%) γ-muurolene (22.7%)	Brazil	ESTEVÃO et al., 2013 (Brazil)
trans-α-bergamotene (10.2%) β-elemene (8.0%) γ-muurolene (16.1%)	Brazil	ZIMMERMAM-FRANCO et al., 2013 (Brazil)
β-caryophyllene (1.1-9.0%) α-cadinol (3.2-7.9%) caryophyllene oxide (7.4-16.6%) spathulenol (12.6-35.7%), bicycle-germacrene (1.5-5.7%) germacrene D (4.0-18.0%)	Brazil	DE ALMEIDA et al., 2016 (Brazil)

*****other country occurrences: Argentina and Paraguay.
****** copaiba oil collected from Brazil. Source: by author

TABLE 9.4
Copaifera cearensis Huber ex Ducke species occurrence and major components.

Major Components	**Country Occurrence**	**Reference and Country of Study**
β-caryophyllene (19.7%) clorechinic acid (11.3%) α-copaene (8.2%) β-bisabolol (8.2%) δ-cadinene (7.2%) hardwickiic acid (6.2%)	Brazil	VEIGA JUNIOR et al., 2007 (Brazil)
β-caryophyllene (19.7%) α-copaene (8.2%) hardwickiic acid (6.2%)	Brazil	SANTOS et al., 2008 (Brazil)
β-caryophyllene (0.7-6.2%) *trans*-α-bergamotene (3.4-7.9%) β-bisabolene (8.9-12.1%) hardwickiic acid (0-24.3%) kaur-16-en-19-oic acid (19.8-24.5%) polyalthic acid (17.1-27.7%) β-selinene (5.5-7.3%)	Brazil	CASCON; GILBERT, 2000 (Brazil)

Source: by author

TABLE 9.5
Copaifera duckei Dwyer species occurrence and major components.

Major Components	Country Occurrence	Reference and Country of Study
β-caryophyllene (25.1-50.2%) *trans*-α-bergamotene (6.4-12.0%) β-bisabolene (5.2–33.6%) (*E*)-β-farnesene (2.9-5.8%) β-selinene (1.8-6.7%)	Brazil	LAMEIRA et al., 2009 (Brazil)
β-caryophyllene (13.0-15.5%) *trans*-α-bergamotene (8.3-10.6%) β-bisabolene (15.7-17.6%) β-elemene (8.3-9.4%) β-selinene (13.8-15.4%) α-selinene (8.8-9.9%)	Brazil	LAMEIRA et al., 2009 (Brazil)
β-caryophyllene (0.7-6.2%) *trans*-α-bergamotene (3.4-7.9%) β-bisabolene (8.9-12.1%) hardwickiic acid (0-24.3%)kaur-16-en-19-oic acid (19.8-24.5%), polyalthic acid (17.1-27.7%) β-selinene (5.5-7.3%)	Brazil	CASCON; GILBERT, 2000 (Brazil)

Source: by author

TABLE 9.6
Copaifera officinalis (Jacq.) L. species occurrence and major components.

Major Components	Major* Country Occurence	Reference and Country of Study
β-caryophyllene (24.9%) *allo*-aromadendrene (7.5%) β-bisabolene (6.3%) δ-cadinene (15.3%) α-cadinene (5.6%) germacrene B (5.1%)	Brazil	DIAS et al., 2014a (Brazil)
β-caryophyllene (8.5%) hardwickiic acid (30.7%) copalic acid (13.9%)	Brazil	SANTOS et al., 2008 (Brazil)

***other country occurrences: Colombia, Venezuela and San Salvador.

Source: by author

TABLE 9.7
Other *Copaifera* species from Brazil occurrence and major components.

Copaifera species	**Major Components**	**Reference and Country of Study**
Copaifera publflora Benth	**β-caryophyllene (65.9%)** β-selinene (10.2%) α-humulene (7.3%) α-selinene (5.5%)	ZOGHBI et al., 2009 (Brazil)
Copaifera trapezifolia Hayne	**β-caryophyllene (33.5%)** germacrene D (11.0%) spathulenol (7.6%) α-humulene (6.2%)	VEIGA JUNIOR et al., 2006a (Brazil)
Copaifera paupera (Herzog) Dwyer	**β-caryophyllene (14.1%)**α-copaene (42.5%) δ-cadinene (10.4%) α-cubebene (5.5%)	ZOGHBI et al., 2009 (Brazil)
Copaifera spp.	**β-Caryophyllene (11.48%)** α-bergamotene (7.04%)	RIBEIRO et al., 2019a (Brazil)
Copaifera piresii Ducke	**β-caryophyllene (10.3%)** α-copaene (45.5%) δ-cadinene (13.7%)	ZOGHBI et al., 2009 (Brazil)
Copaifera guianensis Desf.	caryophyllene oxide (19.1%) kaur-16-en-19-oic acid (17.5%) hardwickiic acid (11.0%) polyalthic acid (10.6%) *trans*-α-bergamotene (7.2%)	CASCON; GILBERT, 2000 (Brazil)
Copaifera lucens Dwyer	polyalthic acid (69.8%) copalic acid (11.1%)	SANTOS et al., 2008 (Brazil)
Copaifera martii Hayne	β-bisabolene (10.7%) kovalenic acid (29.0%) kaurenoic acid (7.9%) zingiberene (7.2%)	SANTOS et al., 2008 (Brazil)
Copaifera paupera (Herzog) Dwyer	β-bisabolene (20.2%) zingiberene (19.4%) kaurenoic acid (13.3%) copalic acid (6.1%)	SANTOS et al., 2008 (Brazil)

Source: by author

Barreto Júnior et al. (2005), Leandro et al. (2012), Dos Santos et al. (2013) and Veiga Júnior et al. (2005) have been shown that specific phytoconstituents could be obtained by a specific chromatography approach with ionic resins who retain carboxylic acids and elute sesquiterpenes and then, sequentially diterpenic acids. Highlighting two examples: i) the ion exchange chromatography was applied to the fractionation of the *Copaifera multijuga* Hayne, in non-aqueous

medium, for separation of basic or acidic fractions from copaiba oil as an important unit operation in preparative scale for commercial purpose. In that study an anionic macroporous resin was successful used for separation of the acid fraction of *C. multijuga* rich in labdanic diterpenes (BARRETO JÚNIOR et al, 2005; LEANDRO et al, 2012; VEIGA JÚNIOR; PINTO, 2002); ii) silica modified with KOH was used to separate diterpenoic acids from a *C. multijuga* sample, aiming at to analyses their biological activity (VEIGA JÚNIOR; PINTO, 2002).

Volatile constituents of *Copaifera langsdorffii* Desf. sample collected from Brazil, were studied by using GC/MS analysis of the hydrodistilled essential oils obtained from leaves, root bark, fruit peel, trunk bark, trunk wood, root wood and fruits, allowing the identification of 40 different constituents. The major compounds of those samples were: β-caryophyllene (53.3% from copaiba balsam oil; 16.6% from leaf oil of and 14.8% from fruit oil); caryophyllene oxide (47.3% fruit peel oil; 40.5% root wood oil; 31.0% trunk wood oil; 30.7% root bark oil); γ-muurolene (29.8% fruit oil; 25.2% leaf oil; 8.3% trunk wood oil); kaurene (30.2% trunk wood oil; 16.7% trunk bark oil; 8.2% root bark oil); 4-α-copaenol (17.6% root wood oil); β-bisabolol (30.5%) and kaurenal (31.9%) from trunk bark oil (GRAMOSA; SILVEIRA, 2005).

From hydrodistillation chemical procedure of copaiba oilresin applied to *C. langsdorffi* and *C. martii*, the sesquiterpenes β-caryophyllene, α-calacorene gleenol and seline-3,7(11)-diene were identified. Indeed, from several samples from *C. langsdorffi*, *C. duckei* and *C. reticulata* collected in Brazil, β-caryophyllene is usually the major constituent. Meanwhile, α-copaene is the major constituent of samples from *C. martii*, *C. paupera* and *C. piresii* also collected in Brazil (ARRUDA et al., 2019; FERRO et al., 2018; LEANDRO et al, 2012; MACIEL et al, 2002; SOUZA et al., 2011a; TINCUSI et al., 2002; VARGAS et al., 2015; VEIGA JÚNIOR et al., 2002).

Regarding to the complex chemical composition of *Copaifera* species oleoresin, several factors can influence the compounds presence and amount, such as genetics, climate and harvesting conditions. Considering these aspects and also the pharmacological properties of copaiba oil, the validation of analytical methods for the quality control of samples is mandatory for the quantitative and qualitative control (ARRUDA et al., 2019).

In this sense, their identifications by using HRGC-FID and HRGC-MS analysis have been performed by comparing the obtained data with those stored in Espectoteca Wiley as well as by substances pattern. Specifically, the chromatography analysis of fractions obtained from copaiba oil (after suffering esterification) are performed following specific conditions such as: i) a gas chromatography equipment (Hewlett Packard-5890 model), S4-54 column with 20 m length, 0.25 mm internal diameter and 0.25 µm thick phase; ii) hydrogen gas carrier gas at a flow rate of 2 mL/min and flow division (split 1:20); iii) initial temperature set at 120 °C with heating rate of 2 °C/min until reach 160 °C, this temperature is selected heating rate 10 °C/min up to 270 °C, and the final temperature is held constant for 5 min. This applied phytochemical methodology was standardized for copaiba oil commercialization (CASCON; GILBERT, 2000; LEANDRO et al., 2012; VEIGA JÚNIOR; PINTO, 2002).

Xavier Júnior et al. (2017) developed a precise method for quantification of the main compounds of copaiba oil (*Copaifera langsdorffii* Desf.) by using gas chromatography mass spectroscopy (GC/MS) method. In that work it was possible to identify diterpenes compounds form both the copaiba resin and its essential oil. Then the GC/MS method was transposed to be used with a flame ionization detector (FID) and validated as a quantitative method. A good correlation between GC/MS and GC/FID was obtained favoring the transposition method. This chemical approach showed satisfactory sensitivity, specificity, linearity, precision, accuracy, limit of detection and limit of quantitation for β-caryophyllene, α-humulene and caryophyllene oxide. Specifically, the main compounds identified in copaiba essential oil were β-bisabolene (23.6%), β-caryophyllene (21.7%)

and α-bergamotene (20.5%). Meanwhile, from the derivatized copaiba resin the diterpenes identified were copalic acid methyl ester (15.6%), β-bisabolene (12.3%), β-caryophyllene (7.9%), α-bergamotene (7.1%) and labd-8(20)-ene-15,18-dioic acid methyl ester (6.7%).

The main non-volatile components belong to the diterpenes class are caurano, labdanum and clerodane skeletons, including kaurenol, kaurenoic acid, copalic acid, agathic acid, and hardwiickic acid (SOUZA et al., 2011a; 2011b). Some copaiba oils such as *C. cearensis* and *C. langsdorfii* could present a high content of kaurenoic acid as it can naturally precipitate forming crystals. For this reason, this diterpene is one of the most studied substance from copaiba oils (LEANDRO et al, 2012).

Sesquiterpenes from copaiba oil of samples colleted from *C. duckei* Dwyer, *C. pauper* (Herzog) Dwyer, *C. piresii* Ducke, *C. publiflora* Benth., and *C. reticulate* Ducke, were identified such as: *cis*-α-bergamotene, *trans*-α-bergamotene, (Z)-α-bisabolene, α-bulnesene, (E)-γ-bisabolene, epi-β-bisabolol, (Z)-γ-bisabolene, *trans*-cadina-1(6),4-diene, *trans*-cadina-1(2),4-diene, β-chamigrene, cubenol, epi-cubenol, β-curcumene, γ-curcumene, cyclosativene, cyperene, 4,5-diepiaristolochene, (E)-β-farnesene, (E,E)-α-farnesene, (Z)-β-farnesene, germacrene A, globulol, guaia-6,9-diene, *cis*-β-guaiene, *trans*-β-guaiene, γ-gurjunene, humulene epoxide II, epi-α-muurolol, epi-β-santalene, 7-epi-α-selinene, 7-epi-sesquithujene, sesquisabinene, valencene and viridiflorene. The main sesquiterpenes identified in copaiba oil samples are β-caryophyllene, caryophyllene oxide, α-copaene, α-humulene, τ-muurolene, β-bisabolene and β-bisabolol. Some such as α-curcumene, δ-cadinene, β-bisabolene, β-elemen, β-caryophyllene and bisabolol (Figure 9.1) have its bioactivities reported wherein α-curcumene and β-bisabolene are antiulcerongenic and antiviral agents; β-bisabolene also shows anti-inflammatory and analgesic proprieties; β-caryophyllene is also described as anticancer, anti-inflammatory and antimicrobial agent (SOUZA et al., 2011a; 2011b; VEIGA JÚNIOR; PINTO, 2002).

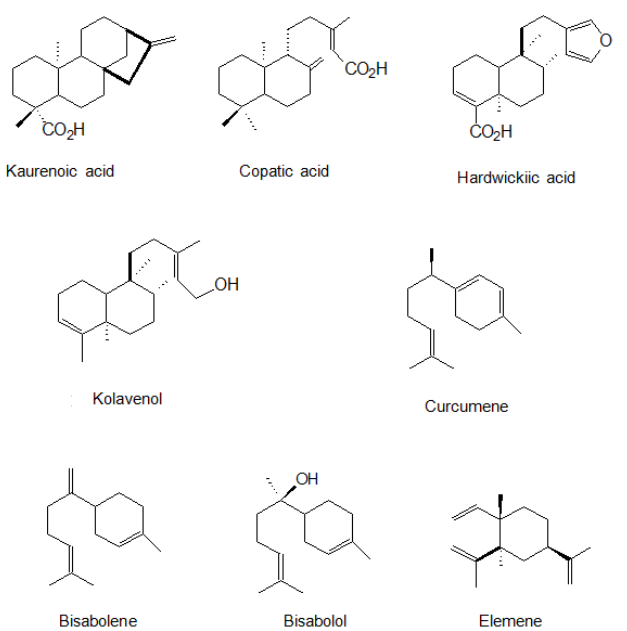

FIGURE 9.1
Some chemical constituent structures from *Copaifera* specimens. Source: by author

Other biochemicals were identified from copaiba oil samples such as xyloglucans oligosaccharides (40.0%), linoleic (35.7%), palmitic (24.9%), oleic (35.3%), behenic (3.00%), araquidinic (1.1%) acids and coumarins (0.15%) (IZUMI et al., 2012; LEANDRO et al., 2012; DOS SANTOS et al., 2013; IZUMI et al., 2012; LEANDRO et al., 2012; VEIGA JÚNIOR et al., 2002; 2005; 2006a; 2006b; 2007).

Although *Copaifera* species have its traditional uses largely described, a restrict biological studies are available for *C. cearensis* Huber ex Ducke, C. duckei Dwyer, *C. langsdorffii* Desf., *C. langsdorffii* Desf., *C. lucens* Dwyer, *C. martii* Hayne, *C. multijuga* Hayne, *C. officinalis* (Jacq.) L., *C. paupera* (Herzog) Dwyer, *C. reticulata* Ducke and C. sp. (commercial copaiba oleoresins). For many reported studies from *Copaifera* species it was not discriminate which comes from commercial copaiba oil or specific plant species (LEANDRO et al, 2012; MACIEL et al, 2002; SOARES et al, 2013; SOUZA et al., 2011a; VEIGA JÚNIOR; PINTO, et al, 2002).

Considering the whole copaiba oil bioactive constituents, the great amount comes from Brazilian *Copaifera* species, and some of them, showed anticancer, antileishmanial, microbiological, antiparasitic, antipsoriatic, among other properties. So, Table 9.8 shows the propose of some studies focusing on copaiba oil chemical composition associated with its biological effects and original country of collected samples.

Regarding to the pharmacological improvement, the antileishmanial activity of several diterpenes isolated from copaiba oil were analyzed in which the 3-hydroxy-copalic acid was observed to be highly bioactive (DOS SANTOS et al., 2013). Similarly, diterpenic acids from copaiba oils had their synergistic effect together with caryophyllene analyzed to chagas disease. The activity was observed to copalic acid, 3-hydroxy-copalic acid and caryophyllene, but also, it was potentialyzed 20 times when copalic acid was put together with caryophyllene (IZUMI et al., 2012).

For a general vision Figure 9.2 shows the lower researches statistics for copaiba oil isolated compounds and its pharmacological applications, in the years 2002 to 2019, which ranges between 2 and 3 published papers by year. Recent statistics reported for both chemical and pharmacological researches performed by using copaiba oil isolated compounds for the years 2016 to 2019, almost doubled by year showing a progressive tendency.

TABLE 9.8
Studies developed with bioactive constituents isolated from copaiba oil applied in healthcare.

Purpose of the study	Pharmacological activity	Reference and Country of Study
Potential cytotoxic and genotoxic effects of the isolated kaurenoic acid and its semi-synthetic derivatives methoxy kaurenoic acid (methyl ent-kaur-16(17)-en-19-oate; MKA) and kaurenol (ent-kaur-16(17)-en-19-ol; KRN) in CHO-K1 cell lines.	Antibacterial and antispasmodic	CANO et al., 2017 (Brazil)
Copaiba oil chemoprevention assessment applied focusing on its some identified compounds, was investigated on DNA damage, pre-neoplastic lesions	Anticancer	SENEDESE et al., 2019 (Brazil)

	and mitotic frequencies induced by the 1,2-dimethylhydrazine (DMH; intraperitoneal injection) carcinogen by comet, aberrant crypt focus (ACF) and long-term assays, respectively.		
	Antibacterial activity of *Copaifera duckei* Dwyer oleoresin and two isolated compounds [eperu-8(20)-15,18-dioic acid and polyalthic acid] against bacteria involved in primary endodontic infections and dental caries.	Anticancer and antimicrobial	ABRÃO et al., 2018 (Brazil)
	Synthetic ent-kaurenoic acid derivatives were obtained by microbial transformation methodologies and tested against breast cancer cell lines (MCF-7).	Anticancer	DA COSTA et al., 2018 (Brazil)
	Genotoxicity and the chemopreventive potential of *Copaifera multijuga* Hayne oleoresin and copalic acid.	Anticancer	ALVES et al., 2017 (Brazil)
	Effect of kaurenoic acid, obtained from copaiba oil resin, in gastric cancer and a normal mucosa of stomach (MNP01) cell lines.	Anticancer	CARDOSO et al., 2017 (Brazil)
	Antibacterial action of the *Copaifera langsdorffii* Desf. oleoresin and (-)-copalic acid, against a multiresistant bacteria as well as their antiproliferative activity.	Anticancer and antibacterial	ABRÃO et al., 2015 (Brazil)
	New small chaperone inhibitors from copaiba oil fractions (copalic acid, hardwickiic acid and 3-acetoxycopalic acid).	Anticancer	LAMA et al., 2014 (USA) (not identified sample origin)
	Genotoxicity evaluation of copaiba oil, their volatile compounds and also the resinous fractions.	Anticancer	ALMEIDA et al., 2012 (Brazil)
	Evaluation of *Copaifera multijuga* Hayne fractions	Anticancer	GOMES et al.,

against ascitic and solid Ehrlich tumor.		2008 (Brazil)
Genotoxicity evaluation of kaurenoic acid.	Anticancer	CAVALCANTI et al., 2006 (Brazil)
Inhibition of lung metastasis and tumor growth induced by melanoma cells using specific compounds rich fractions from *Copaifera multijuga* Hayne.	Anticancer	LIMA et al., 2003 (Brazil)
Effects of kaurenoic acid, a diterpene isolated from the oleo-resin of *C. langsdorffii* Desf. in developing sea urchin (*Lytechinus variegatus*) embryos, on tumor cell growth in microculture tetrazolium (MTT) test and on mouse and human erythrocytes in hemolysis assay.	Anticancer	COSTA-LOTUFO et al., 2002 (Brazil)
In vivo antiedematogenic activity of specific compounds rich fractions obtained from *Copaifera multijuga* Hayne.	Antiedematogenic	VEIGA JÚNIOR et al., 2006b (Brazil)
Antifungal activity of the copaiba oil and its isolated compounds caryophyllene oxide, copalic acid and acetoxycopalic acid against *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Microsporum gypseum* strains.	Antifungal	NAKAMURA et al., 2017 (Brazil)
Protective effect of β-caryophyllene from copaiba oils.	Anti-inflammatory and antioxidant	AMES-SIBIN et al., 2018 (Brazil)
Effects of L-arginine and kaurenoic acid of copaiba oil against ischemia reperfusion injury in a randomized skin flap model in rats.	Anti-inflammatory and antioxidant	SILVA et al., 2015 (Brazil)
In vitro cytotoxicity and anti-inflammatory effects of six diterpene acids: copalic, 3-hydroxy-copalic, 3-acetoxy-copalic, hardwickiic, kolavic-15-metyl ester, andkaurenoic, isolated from the oleoresins of	Anti-inflammatory	VARGAS et al., 2015 (Brazil)

	Copaifera spp.		
	Anti-inflammatory effect of kaurenoic acid from *Copaifera langsdorffi*.	Anti-inflammatory	PAIVA et al., 2002 (Brazil)
	Aantileishmanial activity of diterpene from *C. officinales* (methyl copalate and agathic, hydroxycopalic, kaurenoic, pinifolic and polyaltic acids).	Antileishmanial	DOS SANTOS et al., 2013 (Brazil)
	Caryophyllene from copaiba oils as an effective biomarker in copaiba oils or specific compounds rich fractions derived thereof.	Antileishmanial	SOARES et al., 2013 (Brazil)
	Investigation of leishmanicidal activity of *trans*-β-caryophyllene.	Antileishmanial	DOS SANTOS et al., 2008 (Brazil)
	Antimicrobial, Leishmanicidal, cytotoxic activities and inhibitory aldose reductase of various constituents obtained from *Copaifera pauper*.	Antileishmanial and antimicrobial	TINCUSI et al., 2002 (Brazil)
	Antimicrobial and cytotoxic properties of *C. reticulata* oleoresin and also its specific secondary metabolites.	Antimicrobial	PFEIFER-BARBOSA et al., 2019 (Germany) (sample from Brazil)
	Antibacterial potential of ent-copalic acid against the bacterias *Peptostreptococcus anaerobius* and *Actinomyces naeslundii*.	Antimicrobial	SOUZA et al., 2018 (Brazil)
	Anticariogenic activity of nine terpenes and four sesquiterpenes obtained from *Copaifera langsdorffii* Desf.	Antimicrobial	SOUZA et al., 2011a (Brazil)
	Antimicrobial activity of sclareol, manool, (−)-copalic acid, (−)-acetoxycopalic acid, (−)-hydroxycopalic acid, (−)-agathic acid isolated from *Copaifera langsdorffii* against periodontal bacteria.	Antimicrobial	SOUZA et al., 2011b (Brazil)
	Antinociceptive effect of kaurenoic acid from *Copaifera officinalis* and its mechanism of action, and possible adverse	Antinociceptive	DALENOGARE et al., 2019 (Brazil)

effects, in mice.		
In vitro Schistosomicidal effects of *Copaifera* oleoresins (*C. duckei*, *C. langsdorffii*, and *C. reticulata*) and its isolated terpenes from *C. duckei*.	Antiparasitic	BORGES et al., 2016 (Brazil)
Antiparasitic and synergic activity of β-caryophylene methyl copalate and acids (copalic, 3β-hydroxycopalic, agathic, pinifolic, polyaltic and kaurenoic) from *Copaifera.*	Antiparasitic	IZUMI et al., 2012 (Brazil)
Anti-inflammatory mechanism and antipsoriatic effect of the volatile and non-volatile compounds from *Copaifera langsdorffii* Desf.	Antipsoriatic	GELMINI et al., 2013 (Italy) (sample from Brazil)
Labdane diterpenes copalic acid, 3β-acetoxy copalic acid, 3β-hydroxy copalic acid and *ent*-agathic acid from *C. Langsdorffii* oleoresin *in vitro* assayed against *Mycobacterium tuberculosis* (H37Rv, ATCC 27294).	Antitubercular	SILVA et al., 2017 (Brazil)
Systemic immunomodulation potential of the *trans*-caryophyllene as possible prophylactic agent of leukopenia secondary in the chemotherapy.	Immunomodulator	CAMPOS et al., 2015 (Brazil)
Larvicidal activity of diterpenoids (3-β-acetoxylabdan-8(17)-13-dien-15-oic acid, alepterolic acid, 3-β-hidroxylabdan- 8(17)-en-15-oic acid, andent-agatic acid) from *C. reticulata* Ducke against *Aedes aegypti*.	Larvicidal	GERIS et al., 2008 (Brazil)
In vitro effect of kaurenoic acid from *C. langsdorffii*, analyzed on rat uterine muscle.	Relaxant (smooth muscle)	DE ALENCAR CUNHA et al., 2003 (Brazil)
Ability of copaiba oil and kaurenoic acid to eliminate *Trypanosoma cruzi* forms by infected macrophages through	Trypanocidal	KIAN et al., 2018 (Brazil)

other mechanisms in addition to nitric oxide, reactive oxygen species, iron metabolism, and antioxidant defense.

Source: by author

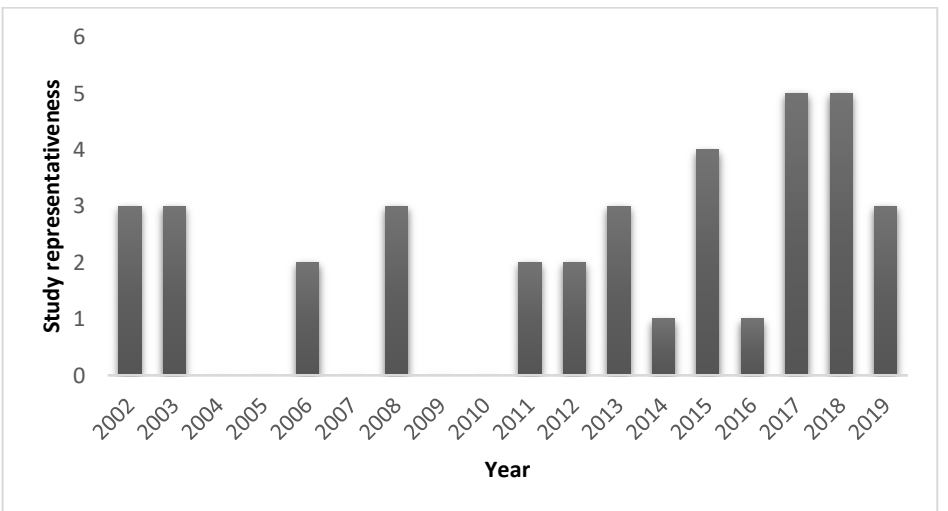

FIGURE 9.2
Statistics reported for chemical and pharmacological researches performed by using copaiba oil isolated compounds in the years 2002 to 2019. Source: by author

Previously to this review article, the chemical and pharmacological progress focusing on the medical potential of copaiba oil were largely assessed for i) occurrence, phytochemistry, pharmacology and analytical methods on *Copaifera* genus (ARRUDA et al., 2019; DA TRINDADE et al., 2018; LEANDRO et al., 2012; PIERI et al., 2009; VEIGA JUNIOR; PINTO, 2002; YAMAGUCHI et al., 2012); ii) evidences for the use of copaiba oil-resin in wound healing (MONTES et al., 2009); iii) chemical composition, biological activities; iv) antimicrobial activity of copaiba oil (*Copaifera* spp.) on oral pathogens (DIEFENBACH et al., 2018; TOBOUTI et al., 2017); v) incremental progress in the treatment of difficult to heal leishmaniasis wounds by using *Copaifera* oil (DE ALBUQUERQUE et al., 2017); vi) meta-analysis on copaiba oil: its functions in metabolismo and its properties as an anti-inflammatory agent (FERRO et al., 2018); vii) topical copaiba oil in treatments for inflammatory arthritis (DINI et al., 2019; HEBERT et al., 2017); viii) copalic acid analogs down-regulate androgen receptor and inhibit small chaperone protein (IDIPPILY et al., 2017); ix) matrix microparticles of *Copaifera langsdorffii* on renal physiology (HENRIQUES BRITO et al., 2017).

Copaiba oil toxicity

Concerning to copaiba oil toxicity, a unique dose of a volatile or resinous fractions obtained from this oil were administered by gavage in rats. The treatment with either one did not increase DNA damage, and there was no alteration in the incidence of micronucleated polychromatic erythrocytes (CHEN et al., 2009). In other study, it was demonstrated that the *C. reticulata* and *C.*

multijuga oleoresin (500 mg/kg by oral route) did not show cytotoxicity in mammalian cells, or induced alterations such as lesions or bleeding in the stomach of treated mice (GOMES et al., 2007; VEIGA JÚNIOR; PINTO, 2002).

Historicaly, *in natura* copaiba oil has been applied since the first colonizers of the Americas who reported its benefits on treatment of navel of newborns and wounded warriors (SILVA et al., 2012a; VEIGA JÚNIOR; PINTO, 2002). Indeed, this medicinal oil is used topically for a variety of painful and inflammatory conditions, including rashes, dermatitis, insect bites, and psoriasis in addition to join pain (HEBERT et al., 2017; RODRIGUES SANTANA et al., 2014).

The anti-inflammatory activity of copaiba oil was correlated to the high content of the sesquiterpenes β-caryophyllene and α-humulene, as well as to the diterpene kaurenoic acid. The anti-inflammatory activity and its mechanism are the most investigated for copaiba oils. This activity was related to the inhibition of the NF-B nuclear translocation, and consequently of proinflammatory cytokines secretion. Indeed, copaiba oil suppressed the proinflammatory cytokines interleukin (IL) 6, IL-8, and IL-1 β in LPS-exposed cells (AMILIA DESTRYANA et al., ARRUDA et al., 2019; BENTO et al., 2011; DIAS et al., 2012; 2014a; HEBERT et al., 2017; SILVA et al., 2002a; 2014; ROGERIO et al., 2009; SARPIETRO et al., 2015).

Silva et al. (2012a) performed a study with 10 patients affected by acne, which receive copaiba oil on a controlled double-blind trial. The findings showed good anti-inflammatory results since improvements occurred in the affected area, and no adverse reaction was reported. According to the medical popular tradition, they also reinforce the milenar practice of copaiba oil use on treatment of navel of newborns. So, this ethnopharmacological study carrying the responsibility for collect answer in sequential fashion critical questions, showed to be both efficient and successful support to the medicinal importance of copaiba oil.

The antipsoriatic effect after oral intake and topical application was also investigated for copaiba oil. In a preliminary clinical trial three patients affected by chronic psoriasis, treated during 6 weeks with oral intake (two patients) and topical application (one patient), exhibited a significant improvement of the disease typical signs, e.g. erythema, skin thickness, and scaliness. Along with the findings, analysis of β-caryophyllene and β-caryophyllene oxide showed their bioavailabilities and absorption effectiveness through cell membranes (GELMINI et al., 2013).

According to Sachetti et al. (2011) higher copaiba oil doses (2 g/kg) did not show neurotoxic effect with a relative margin for safe use as an *in natura* therapeutic agent. Copaiba oleoresin does not pose a health risk to pregnant women when used according to the recommended doses which is up to five drops (730 mg), three times a day (about 2 g of copaiba oil). It seen that copaiba oil for a reduced period administered at control doses is healthy, but on a large amounts or even in the prolonged treatment periods, it may cause side effects such as gastrointestinal irritation, nausea, vomiting, salivation, diarrhea and depression of the central nervous system.

Reinforcing those results, *Copaifera* oils (*C. reticulate*, *C. officinalis* and *C. multijuga*) were applied focusing in wounds treating, such as ulcers scarring and Leishmanial wounds, as well as toxicological assays. The findings showed lower cytotoxicity and genotoxicity (DE ALBUQUERQUE et al., 2017).

Those studies along with the huge phytopharmacological results of copaiba oil brings out safety on practicability of the copaiba oil validation for therapeutic use in the modern medicinal market. Indeed, the strong use of copaiba oil is part of the Brazilian centuries-old folk medicine culture and the biochemical findings summarized in this article unite interdisciplinary scientific fields and largely encourage novel biotechnological approaches, resulting in new challenges for scientific advances of copaiba oil which has been loaded into nanostructured systems, as described in the following section.

Studies designed to bionanoformulations containing copaiba oil

Despite the pharmacological potential of some natural products such as copaiba oil, their poor water solubility remains a challenge on development of effective ecofriendly products. Nanotechnology has emerged as a promising area to solve this problem, especially oil-in-water (o/w) nano or microemulsion type systems. Nanoemulsions containing copaiba oil (*Copaifera multijuga* Hayne) were proposed as a delivery system for copaiba oil in view to treat locally inflamed skin. The SPME-GC method was performed with PDMS (polydimethylsiloxane) fiber (100 µm), by high pressure homogenization. The obtained nanoemulsions were exposed to acid hydrolysis, UV-A irradiation, oxidative (H_2O_2) and thermolitic (60 °C) conditions. Such reduction occurred in lower extent in the nanoemulsions, suggesting the β-caryophyllene protective effect. Since no degradation products were detected in the same retention time of β-caryophyllene, the specificity of the tested process was demonstrated. The method was linear in the range of 0.14-0.68 µg mL(-1) of β-caryophyllene (r(2)>0.999), and was also validated for precision (R.S.D.≤5.0%), accuracy (97.85-101.87%) and robustness. This methodology was validated in the quantification of β-caryophyllene content in the developed formulations (DIAS et al., 2012).

Polar nanoemulsions (o/w) developed by using copaiba oil (*Copaifera duckei*) dispersed through a high internal phase were prepared and evaluated against *Aedes aegypti* larvae. Overall, 31 formulations were prepared, ranging from 11.5 ± 0.2 to 257.3 ± 4.1 nm. Some of them reached small mean droplet sizes (<200 nm) and allowed achievement of a nanoemulsion region. The formulation consisted of 5% (w/w) of oil phase (copaiba oil), 5% (w/w) of surfactant and 90% (w/w) of water, which presented mean droplet size of 145.2 ±0.9 nm and polidispersity of 0.378 ± 0.009. According to larvae mortality level (250 ppm - 93.3 after 48 h) the tested nanoemulsions are available as green ecofriendly larvicidal products (RODRIGUES et al., 2014).

Nanoemulsions produced by high-pressure homogenization and spontaneous emulsification methodology were carried out to obtain stable copaiba oil formulations. The stability of the formulations stored at 4 °C and 25 °C was monitored for 90 days wherein the reduced loss of volatile fraction was observed at 4 °C. Among the tested methods, high-pressure homogenization process proved to be the most efficient technique in which the most suitable nanoemulsion composition was achieved adding 20% of copaiba oil, 10% of medium chain triglycerides, 3% of Span 80® and 1% Tween 20® (a surfactant mixture). The use of medium chain triglycerides was shown to be a good strategy to fix copaiba oil volatile components incorporated into nanoemulsions during preparation and storage (DIAS et al., 2014b).

A copaiba oil nanoemulsified carrier system (CopNEC) prepared by high-pressure homogenization method improved the oral delivery of amphotericin B (AmB) by increasing its oral bioavailability. The optimal CopNEC-AmB (AmB encapsulated CopNEC, d-α-tocopheryl polyethylene glycol 1000 succinate and phosphatidylcholine) had a small globule size, low polydispersity index, high ζ potential and encapsulation efficiency. The high resolution transmission electron microscopy illustrated spherical particle geometry with homogeny in their sizes and the stability of CopNEC-AmB was carried out in simulated gastric fluid and simulated intestinal fluid. CopNEC-AmB was found to be stable in gastrointestinal fluids showing insignificant changes in globule size and encapsulation efficiency. CopNEC-AmB and plain AmB were also compared regarding to the *in vitro* antileishmanial activity, pharmacokinetics, organ distribution and toxicity. CopNEC-AmB synergistically enhance copaiba oil antileishmanial activity. The AUC0-48 value of CopNEC-AmB in rats was significantly improved showing 7.2-fold higher oral bioavailability than free drug. This prototype CopNEC formulation showed improved bioavailability and cause drastic changes in the morphology of Leishmania parasite and rupturing its plasma membrane. Additionally, showed

significantly less haemolytic toxicity and cytotoxicity, had a non-toxic synergistic effect on the antileishmanial activity of AmB, and did not change the histopathology of kidney tissues as compared with plain AmB. In conclusion, the synergistic enhancement of parasiticidal activity of amphotericin B using copaiba oil in nanoemulsified carrier for oral delivery could represent an important approach for non-toxic chemotherapy (GUPTA et al., 2015).

Determination of β-caryophyllene (CAR) skin permeation/retention from crude copaiba oil (*Copaifera multijuga* Hayne) and respective oil-based nanoemulsion using a novel HS-GC/MS method was used as a bioanalytic method gas chromatography in headspace mode coupled with mass spectrometry. It was noted that nanoemulsification of copaiba oil convert this bioresource into a more acceptable hydrophilic formulation and may improve CAR penetration through the skin due to the small droplet size and also by the nanoemulsion higher contact surface. Copaiba oil nanoemulsion presented a better skin penetration compared to the crude oil, with CAR achieving the dermis, the most profound layer of the skin. In conclusion, according to authors, the finding results justify the validation of a novel, sensitive, practical and solvent free methodology, which demonstrate linearity (r(2)>0.99), specificity (no peaks co-eluting with CAR retention time), precision (RSD<15%) and accuracy (recovery>90%) within the accepted parameters and also reinforce β-caryophyllene studies since this compound is one of the major components of copaiba oil and its potent anti-inflammatory property has attracted large attention (LUCCA et al., 2015).

The antimicrobial activity of nanostructured emulsions based on copaiba (*Copaifera langsdorffii*) resin-oil and copaiba essential oil were investigated against fungi and bacteria related to skin diseases. The oils samples were characterized by gas chromatography combined with mass spectrometry (GC-MS). The antimicrobial susceptibility assay was performed followed by the Minimum Inhibitory Concentration (MIC) determination, the bioautography assay, and the antibiofilm determination. Strains of the genera *Staphylococcus*, *Pseudomonas*, and *Candida* were used. Copaiba resin-oil and essential oil nanostructured emulsions improved the antimicrobial activity of the pure oils, especially against *Staphylococcus* and *Candida*, resistant to azoles. The given results showed copaiba oil nanoemulsion samples as a promising candidates for the treatment of infections and also may be used to incorporate other antimicrobial drugs (ALENCAR et al., 2015).

Copaiba oil emulsions (CO) and a suspension of ethanol extract obtained from propolis (EP) were applied on dentin cleaning in order to remove debris that may impair adaptation and marginal sealing. In that investigations through scanning electron microscopy (SEM) the morphology of the dentin surface, cut and treated with CO and EP were performed. The findings showed quantitatively reducing microorganisms. Twenty-four upper pre-molars teeth, divided into eight groups (n=3), were used: G1: no cleaning, G2: air/water spray, G3: 10% CO, G4: 10% CO + A, G5: 30% CO, G6: 30% CO + A, G7: 1% EP, G8: 2% chlorhexidine. The specimens were dentin discs (1 mm Ø). The SEM photomicrographs were classified and the results were: G1 - Debris dentin on the entire image/countless microorganisms, G2 and G7- 50-100 debris / countless microorganisms and G3, G4, G5, G6 and G8-0-50 debris/countable microorganisms (50-100 colonies). In conclusion, both products the copaiba oil emulsions and the suspension of ethanol extract of propolis quantitatively reducing microorganisms and showed feasibility to be used as bioactive dental cleaning agents (BANDEIRA et al., 2016).

Copaiba oil has emerged as an alternative for the inhibition of microorganisms in dental biofilm. In this sense, the *in vitro* antibacterial activity of a gel formulation based on copaiba oil (*Copaifera multijuga*) was assayed against strains of *Streptococcus* sp present in dental biofilm. The oil emulsions were formulated and used with the Brain Heart Infusion agar diffusion method with strains of *Streptococcus mitis*, *Streptococcus constellatus* and *Streptococcus salivarius* isolated from

patients as well as standard strains of *S. mitis* (ATCC903), *S. mutans* (ATCC10449), *S. sanguinis* (ATCC15300) and *S. oralis* (ATCC10557). The study groups were as follows: experimental copaiba oil gel, 1% chlorhexidine gel (positive control) and base gel (negative control). The seeded plates were incubated at 37 ºC for 12, 24 and 48 hours, respectively. The obtained results were analyzed by Shapiro-Wilk and Friedman Tests ($p<0.05$) for non parametric data and the Tukey test was used for pH values with 5% level of significance. The experimental copaiba oil gel and 1% chlorhexidine gel showed antibacterial activity against the tested microorganisms. The copaiba oil gel demonstrated antibacterial activity against all the tested strains of *Streptococcus* sp, suggesting that it can be used for dental biofilm control (SIMÕES et al., 2016).

Copaiba oil (CO) was loaded on colloidal o/w microemulsions in the presence of low surfactant content as following: oil and water mixtures (15:85 and 25:75) were titrated with surfactant blends until a microemulsion formation. Microemulsions containing up to 19.6% and 13.7% of the selected surfactant blends afforded o/w microemulsions with a high volume of the oil phase (CO complex natural oil) in which a specific match of solubility parameters was developed between CO and surfactants aiming at forming colloidal formulations with a high dispersed volume of copaiba oil and low surfactant content. The obtained microemulsion systems were proposed as delivery systems for the oral administration of poorly soluble drugs as well as CO pharmacological investigations (XAVIER JÚNIOR et al., 2016).

Microemulsion systems based on CO aiming at its bioavailability, were used to loaded β-caryophyllene (β-CP). The CO-carrier microemulsion systems (CO-MES) containing plurol oleique (8.5%), labrasol (33.8%), water (47.1%) and CO (10.6%) as well as plurol oleique (18.3%), labrasol (36.6%), water (39.0%) and CO (6.1%), behaved as Newtonian fluids and exhibited low viscosity. The applied pharmacological testes showed antimicrobial and anti-inflammatory activity for the CO-carrier systems containing the bioactive sesquiterpene β-CP. Comparatively, the CO-MES formulation prepared with 6.1% of CO, showed a stronger result against all target microorganisms (OLIVEIRA NEVES et al., 2018).

A hydrogel formulation containing CO nanoemulsion prepared with carbopol and hydroxyeethylcellulose, presented a high retention in epidermis (9.76 ± 2.65 μg/cm^2 as higher result), followed by a smaller retention into dermis (2.43 ± 0.91 μg/cm^2 as higher result). Additionally, presented permeation to the receptor fluid (1.80 ± 0.85 μg/cm^2 as higher result and an anti-inflammatory effect was observed on edema inhibitions in mouse ear edema (67% of higher result) and in rat paw edema (72% of higher result). Histological cuts showed the decrease of infiltration, confirming its anti-inflammatory property (LUCCA et al., 2018).

Solid nanoencapsulation containing copaiba oil as feasible and a promising alternative have been also described. In the earlier studies iron oxide nanoparticles dispersed in copaiba oil were developed with low and high velocity resolution by Mössbauer spectroscopy. The results demonstrated differences of Mössbauer parameters for iron oxide nanoparticles which was correlated to interactions of polar molecules of copaiba oil (kaurinic acid) with nanoparticles' surface (OSHTRAKH et al., 2013).

The *in vitro* antimicrobial activity of solution blow spun poly(lactic acid)/polyvinylpyrrolidone nanofibers loaded with copaiba oil (*Copaifera* sp.) were produced by solution blow spinning (SBS). All prepared compositions were able to produce continuous and smooth fibers by SBS. Neat PLA and four PLA/PVP blends containing 20% (wt.%) of copaiba oil were spun and characterized by scanning electron microscopy (SEM) and by studying the surface contact angle, *in vitro* release rate, and antimicrobial activity. The addition of PVP increased fiber diameter, and decreased the surface contact angle. GC analyzes demonstrated that the main component of the copaiba oil was β-caryophyllene, a known antimicrobial agent. Results confirmed the potential of the fiber mats for

use of in controlled drug release and could lead to promising applications in the copaiba oil biomedical field as well as other bioactives compounds (BONAN et al., 2015).

Cutaneous nanoparticle formulation based on co-encapsulation of imiquimod (approved for the treatment of basal cell carcinoma) and copaiba oil were applied against skin carcinoma. The nanostructured capsule was prepared by high-pressure homogenization using the interfacial deposition method and characterized by average diameter (200 nm), zeta potential (-12mV), pH (6) and drug content of approximately 1 mg/mL, and exhibited homogeneity regarding particle size, high encapsulation efficiency and stability. The antitumor activity was considered satisfactory for human skin carcinoma treatment and was correlated with the applied copaiba-nanostructure system which maintain the skin drug release control (VENTURINI et al., 2015).

Nanoencapsulation containing copaiba oil co-loaded with allantoin (NCOA) based on solid lipid nanoparticles were developed by using a high homogenisation technique and characterized by dynamic light scattering (126.06 ± 9.84 nm), laser diffraction (123 ± 1.73 nm), nanoparticle tracking analysis (homogeneous), multiple light scattering analysis (204 nm), high-pressure liquid chromatography, pH and rheology (Newtonian behaviour). The NCOA was *in vitro* evaluated against the emergent yeasts *Candida krusei* and *Candida parapsilosis*, and the fungal pathogens of human skin *Trichophyton rubrum* and *Microsporum canis*. Antifungal susceptibility showed a MIC90 as following: 7.8 µg/mL against *C. parapsilosis*, 250 µg/mL (*C. krusei*), 1.95 µg/mL (*T. rubrum*). Then, the nanoencapsulation of copaiba oil in the presence of allantoin could represent promising therapeutics for skin infections caused by yeasts and dermatophytes (SVETLICHNY et al., 2015).

The *in vitro* pharmacological evaluation of nanocarriers composed of lamellar silicates and copaiba oil was investigated in order to endometriosis control. Intercalation was confirmed by X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), thermogravimetric analyzes (TGA) and differential scanning calorimetry (DSC). Pharmacological findings showed reduction in the viability and proliferation of endometriotic cell cultures suggesting this nanocomposite system as a promising alternative therapy on oral treatment of endometriosis (BORGES et al., 2016).

A study designed to test nanocapsules containing copaiba oil (400 mg/kg) applied to treat pulmonary arterial hypertension (PAH) was investigated on cardiovascular diseases. A single injection of MCT (60 mg/kg i.p.) was administered according to modulate monocrotaline (MCT) protocol, and measurements were performed after three weeks. MCT promoted a significant increase in pulmonary vascular resistance (PVR), right ventricle (RV) hypertrophy and RV oxidative stress and copaiba nanocapsules significantly reduced RV hypertrophy and oxidative stress. PVR was reduced by *in natura* copaiba oil+MCT but not by copaiba-nanocapsules+MCT. In conclusion, copaiba oil may be an important adjuvant treatment for pulmonary arterial hypertension (CAMPOS et al., 2017).

The bactericidal effect of copaiba oil (*Copaifera multijuga* Hayne) *in natura* or in combination with silver nanoparticles produced by green synthesis using Fusarium oxysporum (AgNPbio) were assayed against planktonic and sessile cells of GBS (group B *Streptococcus agalactiae*) including those resistant to erythromycin and/or clindamycin. The combination of copaiba oil with AgNPbio resulted in a synergistic effect against planktonic cells and biofilm formation, reducing the minimal inhibitory concentration values of both compounds. No hemolytic activity was detected for both compounds. GBS remains a leading cause of neonatal infections and an important cause of invasive infections in adults with underlying conditions. Plain copaiba oil, or in combination with AgNPbio represent new strategies for controlling GBS infections (OTAGUIRI et al., 2016).

It is expected that Brazil become the fifth largest natural drug market. This fact attracted representatives of the pharmaceutical industry and leveraged discussions on the importance of

patent protection to ensure the interests of inventors and society (ZUANAZZI; MAYORGA, 2010). For a general vision, Figures 9.3 show the copaiba oil formulations-type in the period 2009 to 2015 developed for therapeutic applications, and Figure 9.4 highlight the growth of biotechnology studies developed with copaiba oil to be applied as phytomedicines.

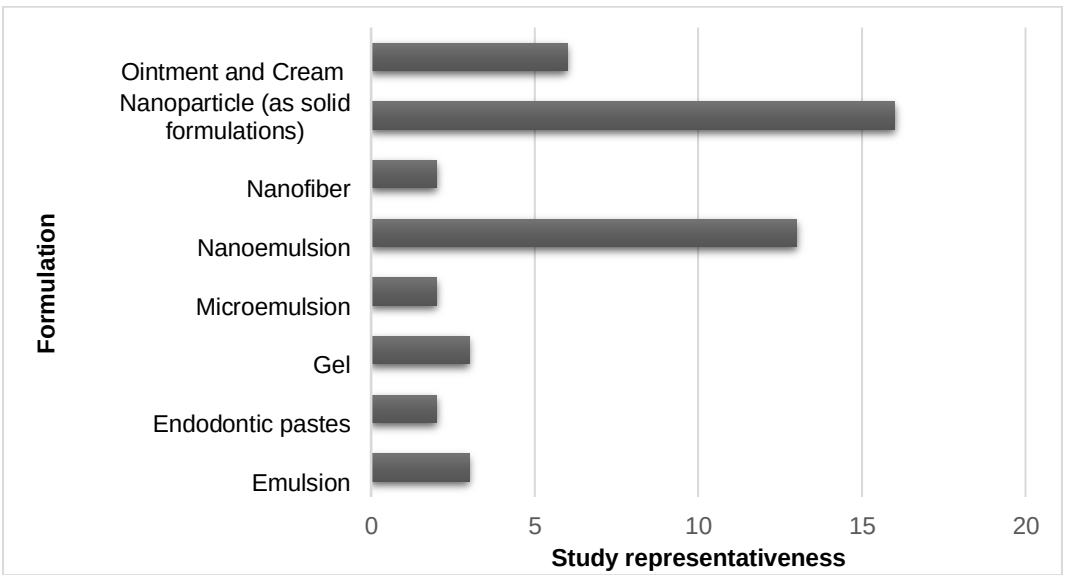

FIGURE 9.3
Copaiba oil applied into different formulations. Source: by author

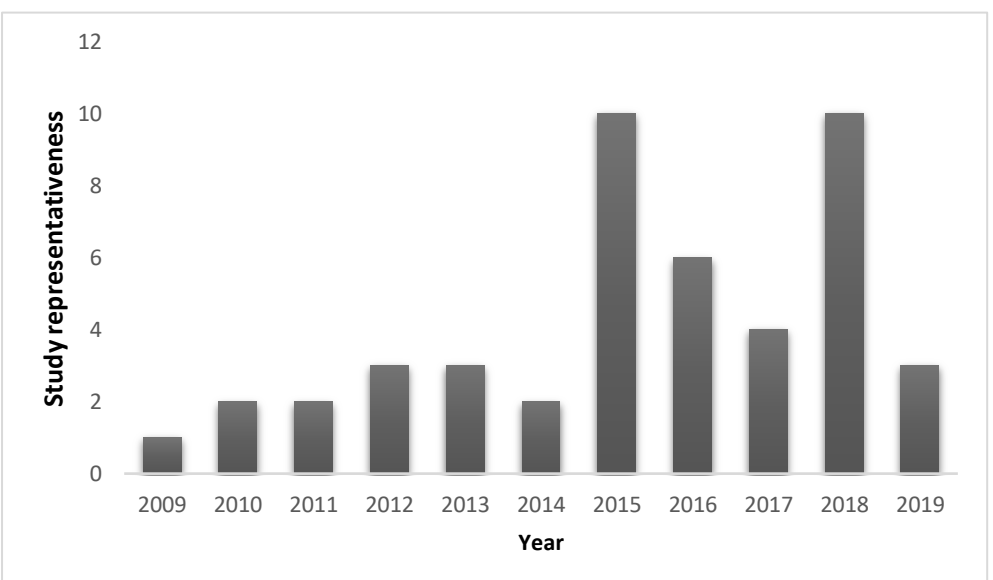

FIGURE 9.4
Representative biotechnology studies growth of the copaiba oil focusing on formulations-type in the period 2009 to 2015, aiming at the healthcare. Source: by author

Comparatively, for the period 2016 to 2019, over than thirty papers have been published for copaiba oil and its isolated or derivatives compounds. This crescent improvement could be addressed such as i) copaiba oil developed nanotechnologies; ii) development of new analytical methods applied in the *Copaifera* oleoresin analysis; iii) difficult challenge to standardize the chemical composition of the main sesquiterpenes and diterpenes copaiba oil compounds. So, recently there are a huge amounts of new publications concerning to copaiba oil focusing on its phytotherapeutic use. Table 9.9 summarizes its foremost medicinal importance, highlighting the main development of copaiba oil loaded into colloidal (gel, emulsion, microemulsion and nanoemulsion) formulations.

TABLE 9.9
Biotechnological and pharmacology results of copaiba oil studies.

Formulation	**Pharmacological Activity**	**Reference and Country of Study**
Cream (vaginal formulation)	Antimicrobial	CARVALHO et al., 2015 (Brazil)
Cream (vaginal formulation)	Antimicrobial	LIMA et al., 2011 (Brazil)
Cream (cutaneous formulation)	Cutaneous wound healing	MASSON-MEYERS et al., 2013 (Brazil)
Emulsion	Antimicrobial	DE BARI et al., 2016 (Brazil)
Emulsion	Antimicrobial	MARANGON et al., 2017 (Brazil)
Emulsion	-	XAVIER JÚNIOR et al., 2012 (Brazil)
Endodontic pastes	Antimicrobial	DIAS et al., 2015. (Brazil)
Endodontic pastes	-	GARCIA et al., 2011 (Brazil)
Gel (inflammation formulation)	Antiacne	SILVA et al., 2012a (Brazil)
Gel (hydrogel formulation)	Anti-inflammatory	LUCCA et al., 2018 (Brazil)

Gel (dental formulation)	Antimicrobial	PEREIRA et al., 2010 (Brazil)
Microemulsion	Antimicrobial and anti-inflammatory	OLIVEIRA NEVES et al., 2018 (Brazil)
Microemulsion	-	XAVIER JÚNIOR et al., 2016 (Brazil)
Nanoemulsion	Anticancer	DE ABREU et al., 2018 (Brazil)
Nanoemulsion	Anti-endometriosis	LUCCA et al., 2015 (Brazil)
Nanoemulsion	Anti-inflammatory	DIAS et al., 2012 (Brazil)
Nanoemulsion	Antileishmanial	RODRIGUES et al., 2018 (Brazil)
Nanoemulsion	Antimicrobial	ALENCAR et al., 2015 (Brazil)
Nanoemulsion	Antimicrobial	VAUCHER et al., 2015 (Brazil)
Nanoemulsion	Antioxidant	EMERENCIANO et al., 2019 (Brazil)
Nanoemulsion	-	DIAS et al., 2014b (Brazil)
Nanoemulsion	Cutaneous anti-inflammatory	HENRIQUES DA SILVA et al., 2015 (Brazil)
Nanoemulsion	Larvicidal	RODRIGUES et al., 2014 (Brazil)
Nanoemulsion	Leishmanicidal	GUPTA et al., 2015 (Brazil)
Nanoemulsion	Leishmanicidal	DE MORAES et al., 2018 (Brazil)

Nanoemulsion	Leishmanicidal	MAZUR et al., 2019 (Brazil)
Solid Nanoparticle (lipid formulations)	Antifungal	SVETLICHNY et al., 2015 (Brazil)
Solid Nanoparticle (cyclodextrin formulations)	Anti-inflammatory	MITSUTAKE et al., 2019 (Brazil)
Solid Nanoparticle (cyclodextrin formulations)	Anti-inflammatory	PINHEIRO et al., 2017 (Brazil)
Solid Nanoparticle (nanofiber formulations)	Antimicrobial	BONAN et al., 2015 (Brazil)
Solid Nanoparticle (silver formulations)	Antimicrobial	OTAGUIRI et al., 2016; 2017 (Brazil)
Solid Nanoparticle (from emulsion)	Antimicrobial	SIMÕES et al., 2016 (Brazil)
Solid Nanoparticle (lipid formulations)	Antineoplastic	VENTURINI et al, 2015 (Brazil)
Solid Nanoparticle (capsules formulations)	Cardioprotective	CAMPOS et al., 2017 (Brazil)
Solid Nanoparticle (nanofiber formulations)	Cutaneous wound healing	MILLAS et al., 2014 (Brazil)
Solid Nanoparticle (chitosan formulations)	Skin burns and other chronic wounds	DEBONE et al., 2019 (Brazil)
Solid Nanoparticle (polyethylene glycol formulations)	Transdermal delivery	QUIÑONES et al., 2018 (Brazil)
Solid Nanoparticle Lipid carriers (NLC)	-	GASPAR et al., 2017 (Portugal) (sample from Brazil)
Solid Nanoparticle (from emulsion)	-	REÁTEGUI et al., 2017; 2018 (Brazil)
Solid Nanoparticle (chitosan capsules)	-	XAVIER JÚNIOR et al., 2018 (Brazil)

Solid Nanoparticle (silicate formulations)	-	DE ALMEIDA BORGES et al., (Brazil)
Solid Nanoparticle (lipid formulations)	-	GARRIDO et al., 2010 (Brazil)
Ointment	Healing	ESTEVÃO et al., 2009; 2013 (Brazil)
Ointment	Healing	GUSHIKEN et al., 2017 (Brazil)

Source: by author

Socioeconomic development of copaiba oil

Markets for products derived from plants (herbal, dietary supplements, cosmetics, insect repellents, dyes, among many other possibilities) are constantly expanding worldwide. It is known that 25% of the drugs currently used in the industrialized countries come directly or indirectly from natural products. So, countries with high biodiversity have the opportunity to go into billionaires' markets such as pharmaceuticals and dietary supplements, which handle about 320 and 31 billion/year, respectively (SOUZA-BARBOSA et al., 2012). In the other hand, the preservation of biodiversity is of paramount importance and can be seen as a way to sustain life on the planet. In Brazil, changes in public health policy are being aligned with the World Health Organization (WHO) recommendations, seeking full and universal assistance to health services, without infringing right to preservation and rational use of biodiversity. So, the importance of plant species for humanity, studies for management, bioprospecting and conservation of the biodiversity are thoroughly carried out (KIM et al., 2012; NOGUEIRA et al., 2010; OLDHAM et al., 2013; WHO, 2014).

Therefore, the appropriation of the biodiversity for industrial purposes is a powerful instrument for sustainable development, since organized and properly performed. In this sense, in the period 1974 to 1979, the state of Amazonas exported 101 tons for domestic market and 433 tons were exported to foreign. In 1992, the exports were about 24 tons of oil to the United States and Europe. During the last century this oil ranked the second place in Brazilian exports of medicinal drugs and represents approximately 95% of the entire oleoresin production country wise and its annual production is around 500 tons/year (ALENCAR, 1982; ALMEIDA et al., 2012; MEDEIROS; VIEIRA, 2008; SANT'ANNA et al., 2007; TAPPIN et al., 2004; VEIGA-JÚNIOR; PINTO, 2002).

By the reason of copaiba oil widespread traditional importance its commercialization had become intense and Brazil became an important exported country to France, Germany and the United States. In fact, this oil was distributed to Europe about 50 tons per year with France responsible for consuming more than 6 tons/year. In this sense, Hamburg and Germany, in the period before the first World War became the main copaiba oil import center to Brazil commercialization. The largest global copaiba oil export period was in the post-war wherein values achieved 225 tons/year. In the very long past, French people was the most dedicated to the study and exploration of copaiba oil. In 1972, the Food and Drug Administration approved the copaiba oil, after being subjected for sensitization and irritation tests on 25 volunteers, with negative results. Along with this application many studies have been performed in order to improve its pharmacological and industrial

importance including wound healing assays (CALLENDER et al., 2017; EMING et al, 2014; GAJENDRAREDDY et al., 2013; GELMINI et al., 2013; MACIEL et al., 2014a; 2014b; ROSIQUE et al., 2015).

The use of natural resources guided by WHO, has stimulate the economies of the developing countries and increased applications for pharmaceuticals and cosmetics patents arising out of the local biodiversity (OLDHAM et al., 2013; WHO, 2013; 2014). Patent is a form of protection of economic and personal interests, in which the state grants a temporary title to the creation (invention or utility model) to the authors, inventors or as individual or entity, regulating and promoting the technological innovation process. In fact, the current model of international intellectual property system favors patent holders, encourages the scientific production and technological innovation. Thus, the analysis of the patent documents is one strategy techniques for monitoring changes and advancements in technology, enabling identification of technological innovation trends over the years (MENELL et al., 2001; MUELLER; TAKETSUMA-COSTA et al., 2014).

Regarding patents involving the copaiba oil, the oldest one is from 1898 (GB189803261) in which copaiba capsules was used in the inflammation treatment of the urethra (gonorrhea). One of the many companies using this oil is the Technico-flor S/A that obtained in France in December 1993 a patent registration (FR2692480) for a "new cosmetic or food compositions including copaiba". In June 1994 achieved the same record at WIPO (WO9400105) expanding it to patent world domination. In the United States, the Aveda Corp achieved in March 1999 a patent registration (US5888251) for a “Method of coloring hair or eyelashes with compositions which contain metal containing pigments and a copaiba resin". The Brazilian Pharmacopoeia describes an ointment containing copaiba oil, for external use, with anti-inflammatory, antiseptic and healing proprieties. The formulation is obtained by mixing 10 g of resin copaiba oil (*Copaifera langsdorffii Desf., C. multijuga H. Kuntze, C. reticulata Ducke* or *C. paupera H. Dwyer*) and 100 g of lanolin and petrolatum ointment.

In the dentistry field, an orthodontic cement containing *Copaifera multijuga* oil a developed product was subjected to laboratory analysis of its chemical and physical properties compared to other three commercial products. The results revealed that the experimental cement complies satisfactorily with the standards of the American Dental Association (GARRIDO et al., 2010).

A considerable number of other patents for therapeutic applications can still be found in the current literature. In that, the number of patents containing copaiba oil for therapeutic purposes or cosmetics uses has increased and some examples are herein highlighted (BR8605738, GB637440, JP07-278001, MU8203234-3, PI1004276-8A). The patent register PI 0404266-2 shows the development of a gel containing copaiba oil to dental application. A patent process (WO2005110446) for preparations of copaiba oil extracts, fractions and isolated compounds from the *Copaifera* species was register for treatment of urinary lithiasis in human beings and animals.

For a general vision, Figure 9.6 shows the number of patents per country that were requested in the period of 1950 to 2019 for copaiba oil aiming at health applications (human or veterinary needs) reported by INPI, EPO, USPTO and WIPO resources. From this amount 27 documents belonged to Brazil, 5 the United States, 6 Chine, 4 Japan, 4 Korea, 2 Spain, 2 Germany and 1 France. However, when considering the copaiba oil commercial products in the last 20 years under patent protection, it was found 17 documents and of these, fourteen were required by Japanese companies and only one was from Brazil (SOUZA-BARBOSA et al., 2012). In the other hand, the growth in the number of Brazilian patents highlights the interest in herbal market and could improve the national biotechnologic management. The Figure 9.7 shows the growth number of patents in the period of 1950 to 2019.

Despite Brazil's leading position in relation to copaiba oil patent requests there was a high number of requests by countries where *Copaifera* is not part of their native flora. Among the patent applicants the participation of foreign companies is a frequent finding and may generate questions about the misappropriation (biopiracy) of natural resources as well as traditional knowledge (OLDHAM et al., 2013).

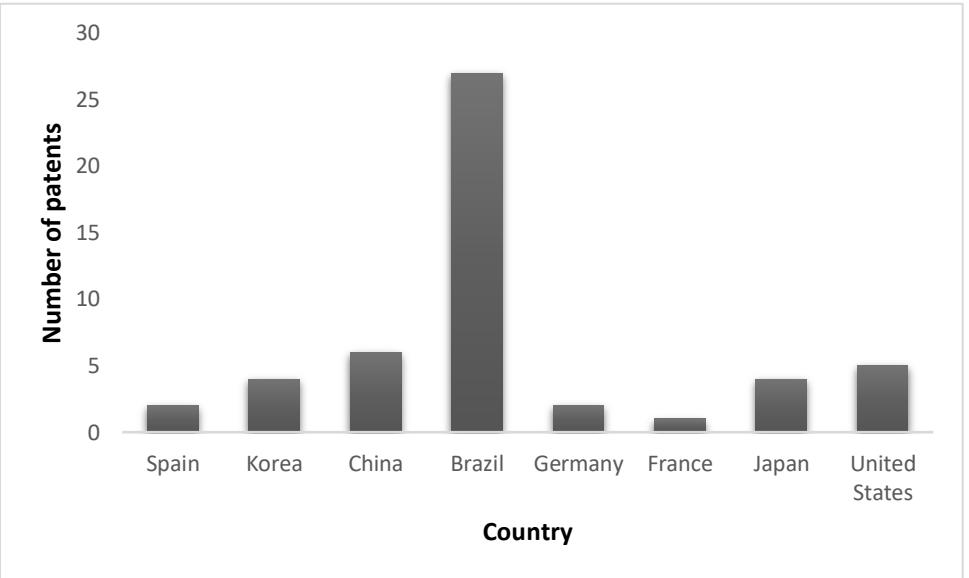

FIGURE 9.6
Number of patents per country requested in the period of 1950 to 2019 for copaiba oil aiming at healthcare. Source: by author

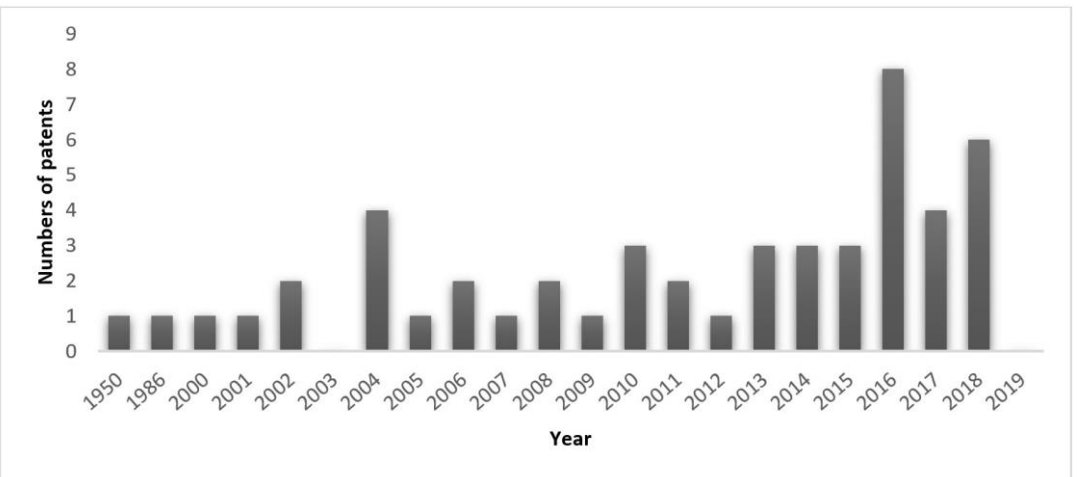

FIGURE 9.7
Numerical growth of patents in the period of 1950 to 2019. Source: by author

Conclusion

Copaiba oil is historically recognized as anti-inflammatory, antimicrobial, analgesic and healing agent, among other medicinal uses. In Brazil, it is largely administered to treat skin lesions, infectious, urogenital, respiratory, gastrointestinal, oncologic diseases, and many other folk indications.

Copaiba oil pharmacological preparations are limited due to its lower water solubility. Nowadays, biotechnology enables the availability and therapeutic uses of some medicinal resources. This is the case of copaiba oil which has been loaded into colloid systems (emulsion, nanoemulsion, and microemulsion), as well as solid nanostructure systems for therapeutic applications.

The pharmacological properties of copaiba oil were correlated with terpenoid compounds such as sesquiterpenes and diterpenes. The main diterpenes components are kaurenol, kaurenoic acid, copalic acid, agathic acid, and hardwiickic acid. The main sesquiterpenes identified are β-caryophyllene, caryophyllene oxide, α-copaene, α-humulene, τ-muurolene, β-bisabolene and β-bisabolol. It is known that β-caryophyllene is described as anticancer, anti-inflammatory and antimicrobial agent. Since this compound has been detected as the main component in several *Copaifera* species, become the most used biomarker to authenticate copaiba oil. Because of that, the anti-inflammatory activity of copaiba oils has been addressed to this compound.

The foremost medicinal use of copaiba oil was designed to skin healing process in which is able to reduce inflammatory response at early stages with significant increase in the fibroblast proliferation phenomena and collagen deposition in wounds.

The market trends investments in copaiba oil biotechnology approach have been justified in order to improve the therapeutic properties of copaiba oil, since it can be limited mainly by its insolubility in water. Therefore, the development of copaiba oil dispersed systems have been seen as a promising strategy, since they allow the delivery of insoluble in water molecules, enhancing its therapeutic effect.

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