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Copaiba Oil for Nano-Pharmaceutics and Drug Delivery

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CONTENTS

1. INTRODUCTION

The Brazilian biodiversity is considered one of the most promising sources of biomolecules, especially those related with the impressive biological activities and potent pharmacological effects observed not only at the Brazilian Amazon region, but also at the Brazilian Savana and Brazilian Atlantic Forest, where a huge biodiversity still being discovered. In spite of the enormous increase in the number and impact of scientific studies performed in Brazil in the last 20 years, the transition from basic science to industry is still waiting to become the real deal of biotechnological development. Considered by some phytochemical scientists as one of the most important plants from Brazil, copaiba (*Copaifera* ssp.) is a Fabaceae plant that exudates a terpenic oleoresin with vast and ancient pharmacological properties. Copaiba trees can be found in several Brazilian biomasses, from Amazonia to South Region, also observed in the western region from Bolivia to Mexico; different species with diverse properties at each region. Extensively used as anti-inflammatory, in healing, and also in cosmetics and perfumery, hundreds of scientific studies with copaiba oleoresins have been performed, but only a few dozen patents have been filed. This review summarizes an integrated phytopharmacological and biotechnological development of copaiba oil aimed at the discovery of new drugs leads from this medicinal plant. Additionally, it describes a worldwide profile of the copaiba patents and focuses the main countries interested in the uses and the evolution of the biotechnological awakening of this herbal medicine.

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2. BIODIVERSITY

Natural medicine has gained popularity, and has not only continued to be used for primary healthcare in developing countries, but also has been used in countries where conventional medicine is predominant in the national healthcare system [1–5]. The increasing use of natural medicine for prophylactic and therapeutic purposes is associated with the limited access of healthcare services all over the world, with higher costs of manufactured drugs and the confirmation of numerous healing properties of plants used in folk medicine [3, 6, 7]. Due to plant's low cost and acceptability when compared to synthetic medicine, medicinal plants and preparations have long been found in civilizations and many cultures around the world. Natural medicines are widely used for production of herbal home-prepared products, as raw materials to drug development in the pharmaceutical industry, and have become a promising resource for the discovery of many biologically active molecules to therapeutic purposes [8–11].

Archeological and historical evidence shows that herbal medicines have been used since the Neolithic Period (about 10,000–12,000 years ago). The Egyptian Ebers Papyrus (1600 BC), one of the oldest documents, describes a large number of animal and vegetable nature drugs to treat over 100 symptoms and diseases [11, 12]. In the Greek civilization before Christ, several philosophers stood up for his works on natural history. Among them Hippocrates, considered the father of modern medicine, for the natural remedies choice (guide in the *Natura medicatrix*). Teofrasto (372 BC), disciple of Aristotle, wrote several books about the history of plants [13]. He recorded the use of botanical species *Papaver somniferu,* whose active ingredient is morphine. Physicians like Galen (129–199 AD), Avicenna (980–1037 AD) and Paracelsus (1493–1541 AD), to name a few, described the therapeutic properties of medicinal herbs in their writings [14]. The isolation of the first pure substances from plants began in the eighteenth century. This century, along with the nineteenth century, is characterized by extracting work of the organic acids and alkaloids, especially. At that time (1806) the alkaloid named morphine was isolated, as well as quinine and strychnine [15]. Since then, traditional medicine comprises practices, approaches, knowledge and beliefs not necessarily based on scientific evidence applied to medical care to diagnose and prevent illness within a society. It is defined by a culture's knowledge and values and thus is context-specific, as are social constructions and negotiations of risk. Therefore, from the second half of the 1970s and 1980s, there was a growth of alternative medicines to treat various diseases using plants, plant parts or their preparations [5, 16]. Medicine based on the premise that plants contain substances that can promote health and alleviate illness with minimal toxic side effects became a crucial tool to increase access to healthcare [17–22].

When modern societies adopt such long-standing health practices outside of the traditional context, these therapies play an important role in non-conventional medicine and, in accordance with the interests of the World Health Organization (WHO), show that over one-third of the population in developing countries lacks access to essential medicines [17, 22–25]. In fact, medicinal plants are used worldwide as self-prescribed home medicines, especially in developing countries, as an aid in primary healthcare in 60% to 80% of the population [26–28]. On the other hand, in developed countries, the population used it at least once: 70% in Canada, 49% in France, 48% in Australia, 42% in USA and 31% in Belgium. On the contrary, when people in developing countries were surveyed about their use of alternative medicine, the values are closer to the global average. In Africa, figures might vary from 60% (Uganda) to 90% (Ethiopia), and the identical situation is observed on the Asian continent, with values around 70% in India [27]. In Latin America, it is similar to what happens with the rest of the developing countries. In Brazil, for example, it has been estimated that only 30% of the population uses conventional medicine [29]. Similarly, in countries such as Bolivia, Ecuador and Colombia, traditional medicine practice was established by the generational transmission of ancestral traditions. Major cities in Argentina show that 70% of the population have adopted alternative herbal medicine [29, 30]. This worldwide characteristic increases in rural areas and traditional communities by unlimited resources or due to geographic isolation or social exclusion [31, 32].

Nowadays, it is estimated that there are 250,000 to 500,000 plant species identified so far; about 35,000 are used worldwide for medical care and, thanks to enormous biodiversity of the planet, the medicinal plants continue to be in vogue and represent a rich source of new, active substances and new drugs for pharmaceutical interests [33–38].

Independent of the number of plants around the world, more than half of living organisms are concentrated in 15 countries such as Australia, Brazil, China, Colombia, Congo, Costa Rica, Ecuador, India, Indonesia, Madagascar, Malaysia, Mexico, Panama, Peru and Zaire. Biodiversity plays an important role in the society and represents a large potential source of, among other things, pigments, dyes, fragrances, aromas, flavors, cosmetics, perfumes, insecticides and medicines [11].

Biodiversity is the variability among living organisms from terrestrial, marine and freshwater ecosystems and the ecological complex, which includes diversity within species, between species and of the ecosystems [39–41]. So, it can be understood as a combination and interaction of various hierarchical components: ecosystem, communities, species, populations and genes in a defined area [42]. According to Dias (2000), biodiversity is one of the fundamental properties of nature, responsible for balance and ecosystem stability and a source of immense economic potential [43].

In Brazil it is estimated that about 2,000,000 different species of animals, plants and microorganisms are inserted into an immense environmental complexity, and distributed in a wide range of ecosystems [40]. In a study realized in 1997, Brazilian biodiversity corresponded to 8,515,767 km^2 of territory, for Brazil harbors 525 species of mammals (among them 75 primates, 32 carnivores, 36 cetaceans), and accounts for 600 amphibians, 468 reptiles, 1,688 birds, 4,450 fishes, 670 mollusks, 4,000 spiders, 26,000 moths and butterflies, 700 termites, 30,000 beetles, 1,500 mites, 3,125 bryophytes, 1,200 to 1,400 pteridophytes, 15 gymnosperms and 40,000 to 45,000 angiosperms [11]. A comparative percentage between Brazil and the world's

known biodiversity is shown in Figure 1, observing Brazil's foremost importance, especially the predominance of bacteria, fungi and bryophyte organisms and angiosperm plants.

Plant biodiversity remains a subject of great importance to discussions related to biodiversity from all other living species on the planet [40]. Brazil is one of the countries with the greatest plant genetic diversity in the world, with about 60,000 species cataloged, and an estimated total of between 350,000 and 550,000 species, which corresponds to about 20% of the world's known flora and 75% of all plant species in the great forests [44, 45].

Currently, traditional knowledge associated with the Brazilian plants biodiversity has become an important tool in the development of new pharmaceutical products for application in the treatment of human diseases [46]. The plants are a significant source of biologically active substances that have an activity on the metabolism of a living organism (different from that in which it was produced), and this substance can constitute a pharmacologic activity [40]. This biological activity comes from the secondary metabolism of plants. The plant's metabolites are related to each variety of plant species and often have particular biological activities. Therefore, the increase in the biological diversity of plant species increases the diversity of chemical substances of vegetable origin that can be obtained and the probability of identifying new biologically active substances [2, 40].

Among bioactive metabolites and their importance stands terpenoids, alkaloids, flavonoids, tannins and phenolic compounds with prominent functions of protection such as antibacterials, antivirals, anti-fungals and insecticides, and against herbivores, by reducing their appetite for such plants, involved in defense mechanisms against abiotic stress (e.g., UV-B exposure), and are important in the interaction of plants with other organisms (e.g., attraction of pollinators). Many of them give plants their odors and flavor (e.g., the capsaicin from chili peppers), and respond to plant pigment such as the case of quinones and tannins [28, 47–50]. Additionally, herbs and spices are largely used by humans to season food, which acts as antioxidant, antibacterial, anti-inflammatory, anti-allergic, hepatoprotective, antithrombotic, antiviral and anticarcinogenic, and they even have vasodilatory and neuroprotective properties [28, 51–53]. Therefore, the diversity in chemical structure and biochemical properties of natural products impress and serve directly or indirectly to the development of a large number of pharmaceuticals [40].

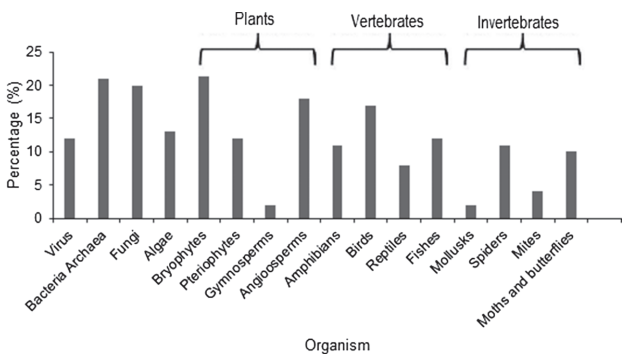

Figure 1. Different species found in Brazil's biodiversity.

In this context, Brazil's biodiversity holds great importance in the function of producing metabolites from six biomes such as the Amazon forest, Atlantic forest, Caatinga, Cerrado, Pampas and Pantanal, according to the detailed distribution observed in Figure 2.

Of concern to the world, the Amazon region is the largest tropical rainforest, and spans across nine countries, including Brazil. The Brazilian Amazon region covers around four million square kilometers, which corresponds to 49.3% of its territory being home to high rates of biodiversity, and also plays a fundamental role in the climate balance of the planet [54–56].

The Brazilian Cerrado (savanna) is the second-largest biome in South America, with an area around two million square kilometers, covering 22% of Brazilian territory. This savanna is formed by a complex set of habitat mosaics and plant varieties that occupy all of central Brazil. Considered one of the world's richest savannas, the Cerrado region represents an estimated 5% of all global biodiversity, with about 12,000 plant species, in which around 4,400 are exclusive to this biome [11, 54].

The Brazilian Atlantic forest (tropical deciduous rainforest) is an environmental complex of mountains, valleys, plains and plateau along the continental coast. Only 12% of this biome remains preserved and it is a global priority for biodiversity conservation [11, 54, 57].

The Brazilian tropical scrub forest is known as *Caatinga,* an indigenous name for "clear and open jungle." Its vegetation is uniquely formed by small woody and herbaceous species, usually carrying thorns, cactuses and bromeliads, and corresponds to an exclusive biome located in the northeastern semiarid region covering 11% of the Brazilian territory. It is estimated that at least 932 plant species have already been registered in this region, of which 380 are exclusive to this biome [11, 54].

The Brazilian Pampa (grassland) is slightly larger, occupying an area of 176,496 km^2, representing about 2.1% of

Figure 2. Distribution of the Brazil biodiversity.

the national territory. This biome is characterized by vegetation composed of grasses, creepers and some trees and bushes found next to waterways. The fields of this biome are an important contribution to the preservation of biodiversity, especially for mitigating the effect of greenhouse gases and helping to control erosion. In the Brazilian section of the biome, around 1,964 species of plants were identified; from that approximately 400 are grasses [11, 58] with an area of 150,355 km^2.

The Brazilian Pantanal (temperate flooded grassland) supports both a rich agricultural and ecotourism economy and consists of a tropical wetland wherein periods of inundation and desiccation alternate annually. Its biome is characterized by grass and a low density of trees, mostly distributed in floodplain areas. The Pantanal area is recognized by UNESCO as a World Natural Heritage Site and Biosphere Reserve [54, 59].

The coastal and marine zone of Brazil occupies around 3.5 million square kilometers. Being one of the longest coastlines in the world, with great diversity and with many exclusive to the Brazilian coast includes mangroves, coral reefs, dunes, salt marshes, beaches, rocky shores, lagoons, estuaries and marshes, and numerous species of flora and fauna [54–59].

This immense Brazilian genetic heritage, already scarce in developed countries, has today priceless economic and strategic value in various activities, especially in the development of new drugs. This statement can be easily confirmed when analyzing the number of drugs obtained directly or indirectly from natural products [60]. Modern therapy consisting of drugs with specific actions on receptors, enzymes and ion channels would not have been possible without the contribution of natural products derived from animal toxins and microorganisms, and especially of higher plants [60].

Plant-derived products have dominated the human pharmacopoeia for thousands of years and have provided an endless source of medicine. Actually, it is estimated that 40% of drugs in the available current therapy have been developed from natural sources with 25% from plants, 13% from microorganisms and 3% from animals [61–63].

In the period ranging from 1983 to 1994, around 520 new drugs were approved by the USA Agency for Food and Drug Control Administration (FDA), wherein 220 (39%) were developed from natural products [61]. It was estimated that one-third of the prescription drugs worldwide were developed from natural products. Another remarkable record for antibiotics and anticancer herbal medicines reaches 70% [61, 64]. The growing interest in plant-derived drugs is associated with the low cost of drug development if compared to the discovery of a synthetic medicine [65].

Although only about 10% of the world's biodiversity has been studied, it is believed that about 140,000 secondary metabolites deriving mainly from higher plants and microorganisms have been isolated and characterized but have not yet been biologically evaluated [66]. This fact indicates that a significant portion of this biodiversity, because of its complexity and of human exploration that causes damage, may never be known. Therefore, pharmaceutical companies searching for drug production produce new substances that can be incorporated into the already-developed products as well as to the development of safe new herbal medicines [67–69]. In that, the efficacy and quality control become important concerns for both consumers and health authorities [4].

Historically it is known that several traditional medicines have been developed in different cultures without international standards and appropriate methods. This standardization is important to ensure a controllable chemical profile due to complexity of the molecules present in plants, and to represent safety to ensure the quality of bioproducts and control plants uses. Because the chemical profile of medicinal plants can be affected by the conditions of cultivation, manufacture, marketing and distribution, it is known that metabolite biosynthesis undergoes variation due to physiological, genetic and environmental (light availability, nutrients, moisture and weather conditions) differences [3, 4, 70–74]. Additionally, the harvest time, storage conditions, drying, extraction methods, processing and packaging of a product could modify the chemical composition of the herbal medicine product. Also included were factors such as pH, temperature, enzyme reactions, the presence of light and metal ions. In most cases, the degradation reactions are occuring such as hydrolysis or oxidation reactions, which are favored by the presence of water in the liquid extracts. Thus, to maintain the biochemical stability it is necessary to establish higher quality criteria in order to ensure development and standardize process parameters [75–77].

In the face of Brazil's megadiversity, copaiba oil is a vast resource from Brazil's biodiversity with potential use in medicine for the treatment of numerous pathologies.

The chemical composition and pharmacological properties of the very efficient medicinal *Capaifera* species were investigated according to the ethnopharmacological approach and showed to be efficient and successful. Copaiba oil has a unique sesquiterpene and diterpene chemical composition which demonstrated several biological effects including antileishmanial and antiparasitic activities, among many other properties [3, 52, 78–80]. In fact, biotechnological studies developed with copaiba oil is a strong representative example of a natural resource application. This happy situation was possible because a worldwide multidisciplinary team was involved in getting the research done correctly.

3. HISTORIC ASPECTS OF COPAIBA OIL

Nowadays traditional knowledge, particularly concerning to Amazonian biodiversity products, includes copaiba oil as an important source of natural substances. This oil has been obtained from trees of the *Copaifera* genus, which has been used in folk medicine since ancient times. The genus *Copaifera*, classified in the family Leguminosae, sub-family Caesalpinoideae, tribe Detarieae, is distributed throughout Africa, Central America, South America, and probably Asia [81]. In Brazil, the *Copaifera* tree is commonly known as copaibeira, pau-de-óleo, copaúva, copai copaibarana, copaibo, copal, marimari and bálsamo dos jesuítas, Kupa'iwa, Kupa'ü (Tupi) and cupay (guarani) [82–86].

According Index Kewensis (1996) there are 72 described *Copaifera* species and only 17 have been chemically studied with analyses limited to the copaiba oleoresin [3, 52, 87–90]. These species are endemic in both the Brazilian Amazon

rainforest and the Cerrado region, being expressive in the Brazilian Amazon where nine plant types can be found such as *C. reticulata* (Ducke), *C. duckei* (Dwyer), *C. glycycarpa* (Ducke), *C. martti* (Hayne), *C. guyanensis* (Desf.), *C. multijuga* (Hayne), *C. piresii* (Ducke), *C. publiflora* (Benth) and *C. paupera* (Herzog) [90].

In the whole world, the most abundant *Copaifera* stands out: *C. officinalis* L. from the Amazon region of Colombia, Venezuela and San Salvador; *C. guianensis* Desf. (Guyana), *C. reticulata* Ducke and *C. multijuga* Hayne from Brazilian Amazon region; *C. confertiflora* Benth (Piauí state city of Brazil), *C. langsdorffii* Desf. from Brazil, Argentina and Paraguay; *C. coriacea* Mart. (Bahia state city of Brazil); *C. cearensis* Huber ex Ducke (Ceará state city of Brazil) [91–94]. The most used *Copaifera* to obtain copaiba oil are *C. reticulate* (with 70% of production), *C. guyanensis* (10%) and *C. multijuga* (10%) [95]. In spite of that, in Brazil, *C. langsdorffii* Desf. is particularly important since it is distributed throughout the country (from Amazon to Santa Catarina, in the Northeast and Midwest) and has four different varieties (*C. langsdorfii* var. grandifolia, grandiflora, slack and glabra) [96].

According to some authors *Copaifera* trees can be characterized as aromatic bark; compound and petiolate leaves with 1–12 pairs of leaflets; paniculate inflorescences with small flowers, numerous and sessile, arranged in spikes; sepals four; ten stamens usually, ovaries with two eggs; dried fruit with two valves, generally smooth, with subfibrous endocarp; lonely seeds, glossy and covered with yellow aryl rich in lipids. The trunk is rough, dark coloring, measuring 0.4 to 4 meters in diameter. The copaibeiras are slow-growing trees, reaching 25–40 feet tall and can live up to 400 years [97–101].

Copaiba oleoresin is a transparent liquid whose color ranges from yellow to light brown and in biological terms, being a product of excretion or detoxification of the plant organism which acts as a plant defense against animals, fungi and bacteria, but also may often affect the organisms who feed on them [102–105]. This oil is biosynthesized in parenchyma cells, lining pockets in leaves, young stems and elongated canals in the trunk. Both pockets and canals are created by schizogeny, e.g., separation of cells to create inter-cellular space or lumen into which resin is secreted [106]. These ducts are located in concentric circles in secondary wood that may delineate seasonal growth and the oleoresin may also accumulate in lysigenous cavities formed by secretory cell breakdown. These cavities may connect and enlarge in the trunk to hold liters of oleoresin [98, 107, 108].

Copaiba oil extraction by cutting into the trunk with an axe is an old practice that causes plant damage. Nowadays, a technique through an auger hole around a meter high has been considered non-aggressive and a most widely used practice. In this process, the auger hole cuts the tree to the center of the stem, 20 cm to 50 cm deep, wherein the oleoresin leaks slowly through the hole. After collection, the holes are closed with bungs of wood from the same tree plus clay, allowing for regeneration and continuing oleoresin production [90, 98, 109–111]. Despite recommendations for copaiba oil extraction and higher extraction depending on methodology, it is considered that production ranges from 0.3 to 3 L/tree, but it could occasionally produce 30 L/tree in a single collection or by a pump for sucking oil in which 4 to 50 liters is expected. Studies in central and western Brazil showed mean copaiba oleoresin yield was less than one liter per tree in trees drilled for the first time, declining in successive harvests in ways a harvester should approach a tree. According to Alencar (1982), the average production in a five-extraction procedure ranged from 235 mL in the first extraction to 34 mL in the fifth extraction. One of the trees came to present 3,500 mL in the second extraction, after producing only 400 mL in the first exploration [98, 109–114].

4. PHYTOCHEMICAL AND PHARMACOLOGICAL ASPECTS OF COPAIBA OIL

The medicinal use of the oil of copaiba has spread to all regions of Brazil. It is taken orally, topically administered and also as a cream. In the northern states of Brazil, the practice of topical administration to treat sore throats is pretty common. Copaiba oils have been widely used as a relevant phytotherapic in traditional medicine being indicated as a stimulant, diuretic, purgative, expectorant, healing, antitetanic, antihemorrhagic, anti-inflammatory, antiulcerogenic, an antiseptic of the urinary system, a treatment of bronchitis, syphilitic illness, skin disorders, leucorrhoea, psoriasis, diarrhea, urticaria, dysentery, infections of the pulmonary and urinary systems, and it even combats different types of cancer. Despite side effects, gastrointestinal irritation, diarrhea, sialorrhoea and depression of the central nervous system caused by high dosages of the oil, its popular use has been intensified [3, 80, 90, 93].

Plant materials are usually complex mixtures which contain several molecules of different sizes with varied functional groups, and become a challenge to the chemist of natural products. Copaiba oil chemical composition, color and viscosity varies according to species and regions [115, 116]. Seasonal differences were observed in *Copaifera multijuga.* This showed that composition variations in temperature and moisture can influence oleoresin production and yield in the copaiba oils collected from the same tree at different times of the year (summer to winter) [116]. Studies developed with *Copaifera multijuga* showed variations in the composition of collected oils from the same tree at different times of the year (summer to winter) [90, 117]. The oleoresin yield may peak in the rainy season for *C. venezuelana* and *C. pubiflora* Benth. These oils exhibit greater fluidity, mainly due to a higher amount of water. The dry season harvest seems optimal for copaiba oil extraction from *C. officinalis* (Jacq.) L. and *C. reticulate* [118, 119], and to some undesignated species in Acre (a state of Brazil) from which the oil is more dense [113]. In addition, it is known that if the same tree is exploited in different periods it may produce different oil quality including yield, color, density and modification on chemical components [90, 97, 120]. Despite these variations, the substances detected were basically the same, but with different concentrations. Since composition variation can be associated with abiotic factors (such as insects and fungi), light and soil nutrients [121–123], many authors attribute

also the variability of these components to the mixture of oils of different botanical species, or specimens of different ages and growing in different places, misidentification of species, or in the case of commercial oils, problems of counterfeiting/adulteration by mixing the other types of oils of lesser value [3, 80, 90, 117]. In that context, it was not confirmed that extraction according to day or hour cause significant variations; it still controversial.

Since the 16th century, copaiba oleoresins have been applied by folk medicine of the north and northeastern regions of Brazil and have been cited as the most commonly used natural products among the population of the Brazilian Amazon region [124, 125]. Among American Indians copaiba oils were used for healing wounds; this property probably was sourced by observing animals rubbing themselves on copaiba tree trunks to heal their wounds [126]. The export of the copaiba oleoresin to Europe has been recorded since the 18th century, ranking second place in Brazilian exports of the medicinal drugs [127]. At that time, it was common for entire indigenous communities be occupied with copaiba oil extraction and its marketing [128].

Copaiba oil's anti-inflammatory property has been reported since the first colonizers of the Americas who reported that the Indians applied copaiba oil to treat navels of newborns and wounded warriors [129].

Long ago, the French were the most dedicated to the study and exploration of copaiba oil. Hamburg Germany, in the period before the first World War, was the main copaiba oil import center from Brazil. The oil was distributed to Europe about 50 tons per year with France responsible for consuming more than 6 tons/year [130]. In the post-war period the largest global copaiba oil export values achieved 225 tons/year [131].

In 1972, the Food and Drug Administration approved copaiba oil after being subjected to tests for sensitization and irritation using 25 volunteers, obtaining negative results for both [132, 133]. By reason of its traditional and widespread use, the commercialization of copaiba oil or its capsule formulation had become intense, being exported to France, Germany and the United States [90, 126]. According to Alencar (1982), in the period from 1974 to 1979, the state of Amazonas (Brazil) exported 101 tons for the domestic market and 433 tons were exported to foreign [98]. In 1992, the exports were about 24 tons of oil to the United States and Europe [134]. So, during the last century, this oil ranked second place in Brazilian exports of medicinal drugs. Nowadays, copaiba oil represents approximately 95% of the entire oleoresin production country-wide and is considered socially and economically significant; several communities still depend on its extraction for their livelihoods [135, 136]. According to the most recent silviculture data published by the Brazilian Institute of Geography and Statistics (IBGE), the search for this raw material is still growing. In 2001, copaiba oil extraction corresponded to 414 tons and in 2003 it was 463 tons, after that the annual production was around 500 tons/year [137–139].

A standard methodology of copaiba oil characterization, or for its authenticity, gas chromatography high resolution analyses using flame ionization detection (HRGC-FID) and mass spectrometry (HRGC-MS) is recommended [52, 90, 115]. From this knowledge it is known that diterpenes and sesquiterpenes are the biomarkers of copaiba oil. In that, sesquiterpene composition was divided on oxygenates and hydrocarbons chemical groups [140, 141]. The traditional chromatographic fractionation methods using normal phase silica-based adsorbents is a difficult approach to separate diterpenes from sesquiterpenes. The carboxylic acids usually adsorb to silica and make its separation and purification harder to obtain. A hydrophilic characteristic of the carboxylate group could be used to reverse phase separations, but is usually inefficient. In the successful chromatographic profile of copaiba oil resin by a gas chromatograph after derivatization reaction, it is possible to identify two well-defined elution groups: sesquiterpene, characteristic of lower molecular compound weight, and the second group identified as diterpenes compounds.

The copaiba oil chemical components identification by HRGC-FID and HRGC-MS analyses is performed by comparing the obtained spectra with those stored in Espectoteca Wiley and substances pattern data which are sesquiterpenes copaiba oil biomarkers. Specifically, the chromatography analysis of fractions obtained from copaiba oil (after suffering esterification) were performed on a gas chromatography (Hewlett Packard-5890 model), S4-54 column with 20 m length, 0.25 mm internal diameter and 0.25 μm thick phase; the following conditions: hydrogen gas carrier gas at a flow rate of 2 mL/min and flow division (split 1:20). The initial temperature was set at 120 °C with heating rate of 2 °C/min until reaching 160 °C, as this temperature was selected heating rate 10 °C/min up to 270 °C. The final temperature was held constant for 5 min. This applied phytochemical methodology was standardized for copaiba oil commercialization and herein is presented as Figures 3–5 [3, 52, 90, 115].

As a general comment, complex mixtures of terpenic and terpenoids compounds come from two groups of distinct biosynthetic pathways [142–145]. Terpenes are made from combinations of several isoprene precursors: isopentenyl pyrophosphate and dimethylallyl pyrophosphate. The mevalonate route operates in the cytoplasm and mitochondria, and the deoxyxylulose pathway in the plastids and sesquiterpenes ($C_{15}H_{24}$) and diterpenes ($C_{20}H_{32}$) are formed in the cytoplasm and plastid organelles, respectively, after modification of the terpene specific synthetases [145, 146]. Aiming at understanding the genetic complexity of terpene biosynthesis in *C. officinalis*, a cluster analysis of sesquiterpenes from different tissues was applied to the major sesquiterpenes: germacrene D, (E)-β-caryophyllene, β-bisabolene, and δ-cadinene. In that, a schematic mechanism for biosynthesis from their common precursor farnesyl diphosphate [(E,E)-FPP type] was proposed [143].

The sesquiterpenes and diterpenes (labdane, clerodane and kaurane skeletons) are different for each *Copaifera* species and have been linked to several reported biological activities, ranging from anti-tumoral to embriotoxic effects. Some sesquiterpenes, such as α-curcumene, δ-cadinene, β-bisabolene, β-elemen, β-caryophyllene and bisabolol (Fig. 6), have its bioactivities reported wherein α-curcumene and β-bisabolene are antiulcerongenic and antiviral agents. Additionally, it is known that β-bisabolene has also anti-inflammatory and analgesic proprieties. Bisabolol was recognized as responsible for the anti-inflammatory and analgesic

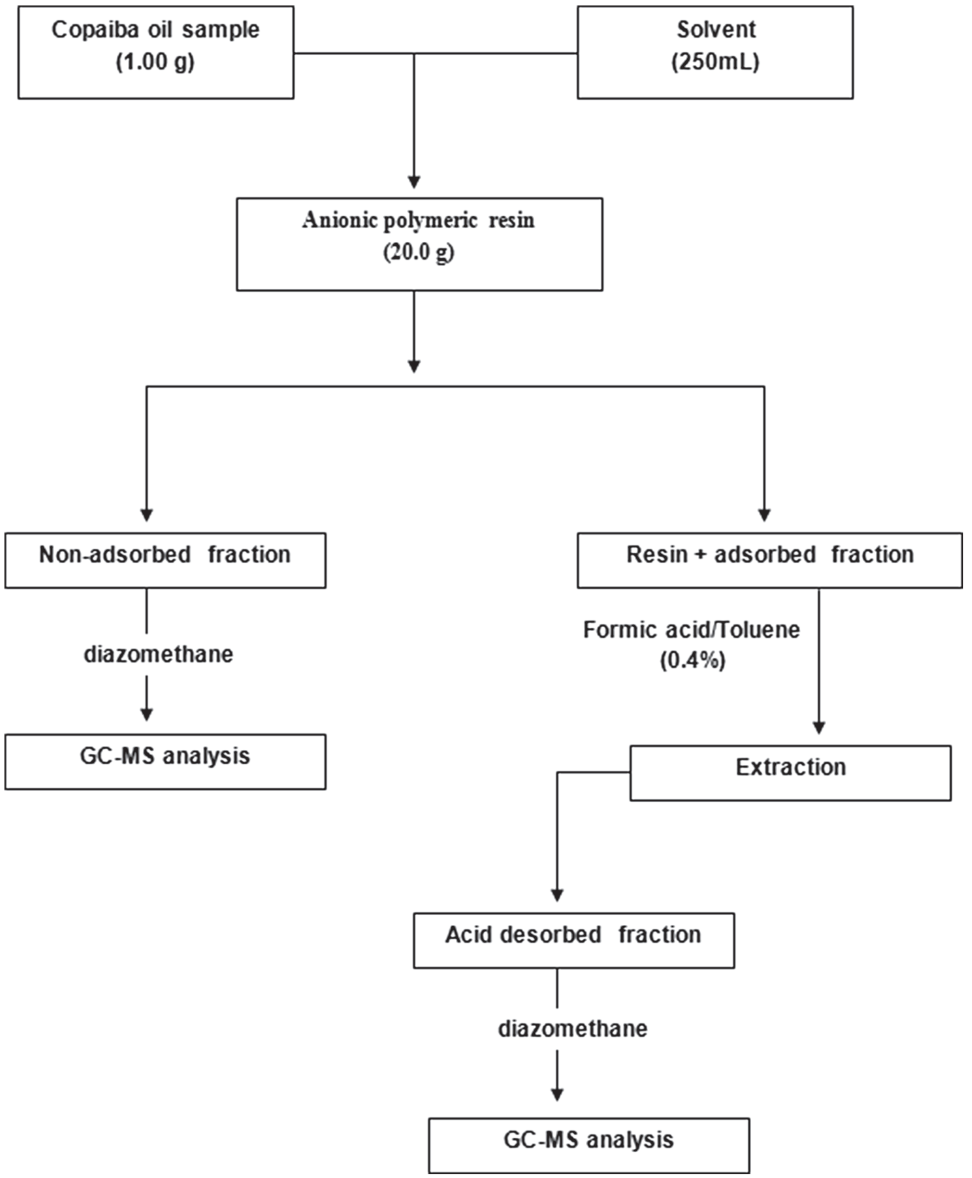

Figure 3. Phytochemical methodology applied in the chemical characterization of the biomedicine copaiba oil.

characteristics of *Matricaria chamomilla* (chamomile). The sesquiterpenes δ-cadinene, β-elemen, and β-caryophyllene are cited as anticarcinogenics agents. For β-caryophyllene, the following properties were also evidenced: anti-edemic, fagorrepelent, anti-inflammatory, antitumoral, bactericide, insecticide, and spasmolitic. Some of those activities were granted based on the oxide caryophyllene [3, 52, 82, 90, 102, 110, 111, 115, 125].

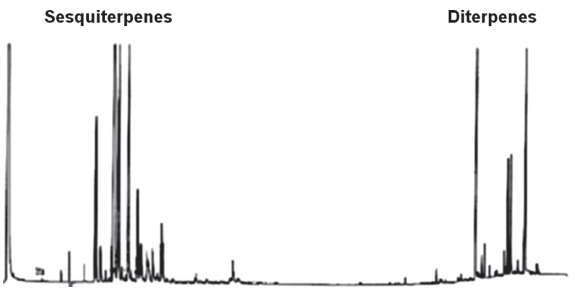

Figure 4. Chromatogram of the esterified copaiba oil.

For a general vision, Figure 7 shows the lower research statistics observed for copaiba oil isolated compounds, which ranges between two and three published papers, and Table 1 focuses mainly on its already identified components. According to some authors, there are 72 sesquiterpenes and 28 diterpenes described from copaiba oleoresin composition, depending on the source. However, only a few species from *Copaifera* have a full study developed for chemical composition identification from the resin and volatile fractions, wherein both the presence and concentration of copaiba oil components are often conflicting [90, 110, 125, 137, 147–149]. It is justified as discussed for environmental factors, plant age, number of harvests and the stage in the

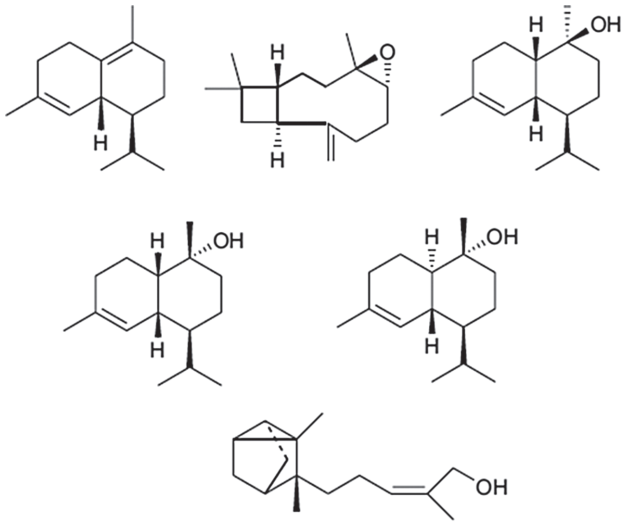

Figure 5. Some sesquiterpenes biomarker structures of copaiba oil.

vegetative cycle. On the other hand, the differences chemical composition may be related to the sensitivity of the analysis method [73, 74].

Athough *Copaifera* species have had their traditional uses largely described, a restricted biological study is 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). In a general context, for many *Copaifera* species, reported studies did not discriminate which were commercial copaiba oleoresins or plant species type [3, 52, 90, 149].

Some review articles listed both sesquiterpenes from copaiba oleoresins. Among them it was found: sesquisabinene, 4,5-diepiaristolochene, germacrene A,

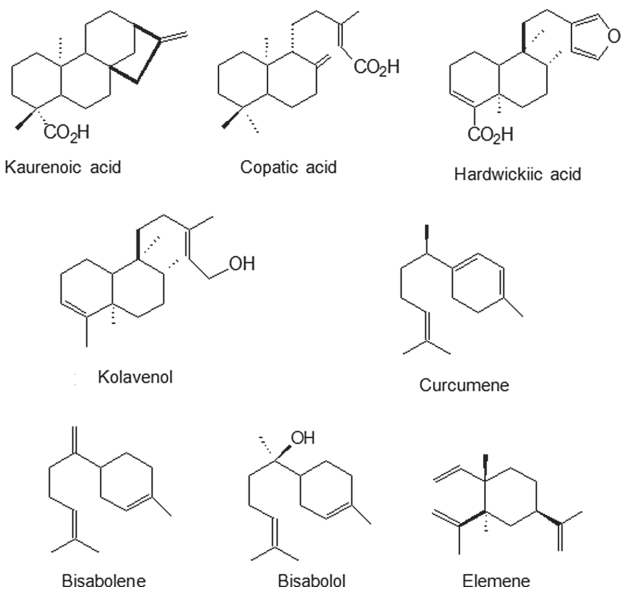

Figure 6. Chemical structures of the chemical constituents obtained from *Copaifera* L.

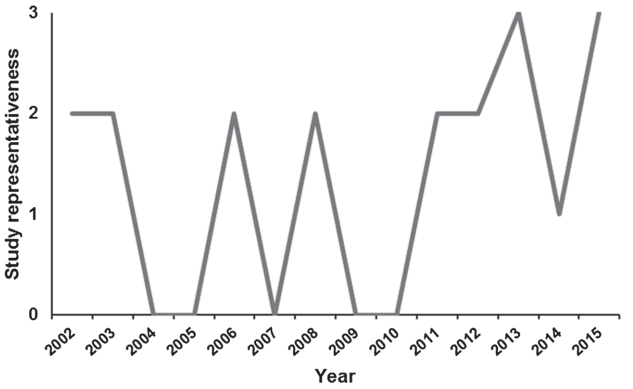

Figure 7. Recent statistics for research performed with copaiba oil isolated compounds.

trans-cadina-1(6),4-diene, β-chamigrene, cis-β-guaiene; viridiflorene, γ-gurjunene, γ-curcumene, epi-cubebol, valencene, *trans*-β-guaiene, (E,E)-α-farnesene, (Z)-α-bisabolene, α-bulnesene, β-curcumene, (Z)-γ-bisabolene, 7-epi-α-selinene, *trans*-cadina-1(2),4-diene, (E)-γ-bisabolene, globulol, humulene epoxide II, epi-cubenol, cubenol, epi-α-muurolol, epi-β-bisabolol, cyclosativene, 7-episesquithujene, cyperene,*cis*-α-bergamotene, *trans*-α-bergamotene, (Z)-β-farnesene, guaia-6,9-diene, epi-β-santalene, and (E)-β-farnesene, coming from *C. duckei*, *C. paupera*, *C. piresii*, *C. pubiflora* and *C. reticulata*. From a hydrodistillation procedure from copaiba oilresin of the species *C. langsdorffi* and *C. martii*, three sesquiterpenes were identified: seline-3,7(11)-diene, α-calacorene and gleenol. In that study β-caryophyllene was usually the major constituent and has been considered a chemical marker of copaiba oleoresins. On the other hand, α-copaene was the major constituent of samples from *C. martii*, *C. paupera* and *C. piresii* collected in Brazil. Meanwhile, β-bisabolene was the major constituent in several samples of *C. duckei* and *C. reticulate,* also collected in Brazil [52, 90, 149, 150, 151]. Table 1 focuses some of the main copaiba oil components.

Among the volatile compounds of the oleoresin characterized by GC/MS are the sesquiterpenes β-caryophyllene, caryophyllene oxide, α-copaene, α-humulene, τ-muurolene, and β-bisabolol [90].

The main non-volatile components belong to the diterpenes class with kaurano, labdanum and clerodane skeletons, such as kaurenoic acid, kaurenol, copalic acid, agathic acid, and hardwiickic acid were detected [150]. For a copaiba oil diterpenes overview it was found for kaurane-type skeletons compounds such as *ent*-kaur-16-ene, *ent*-kaur-16-en-19-al, 19-*nor*-kaur-16-en-4α-ol, and *ent*-kaur-16-en-19-ol, among other ones. For labdane-type skeletons: ent-4-epi-agathic acid, 3-hydroxycopalic acid, 3-acetoxy-copalic acid, 14,15-dinorlabd-8(17)-en-13-one, (−)-13(R)-14,15-dinorlabd-8(17)ene-3,13-diol, (−)-3-β-hydroxy-15,16-dinorlabd8(17)-ene-13-one, (−)-15,16-dinorlabd-8(17)-en-3β,13-diol, and pauperol, among other ones. For clerodane-type skeleton: clerodan-15,18-dioic acid, 7α-acetoxyhardwickiic acid and 7α-acetoxybacchotricuneatin D, among other ones [52, 90, 149–151].

From those phytochemical studies it was realized that chromatography modification procedures improved copaiba

Table 1. Main components of different *Copaifera* oilresin.

Compounds	*Copaifera multijuga* Hayne [147]	*Copaifera multijuga* Hayne [137]	*Copaifera multijuga* Hayne [148]	*Copaifera cearensis* Huber ex Ducke [147]	*Copaifera reticulata* Ducke [147]
Sesquiterpenes					
α-Elemene	0.3	0.2	–	–	0.4
α-Cubebene	0.3	0.6	0.7	1.8	0.4
(+)-Cyclosativene	–	–	–	–	–
α-Ylangene	–	–	0.1	–	–
α-Copaene	2.5	4.2	5.7	8.2	3.0
β-Elemene	–	–	1.2	–	–
β-Cubebene	–	1.4	–	3.3	–
Cyperene	–	–	–	–	–
α-Cedrene	1.1	–	–	–	1.5
α-Gurjunene	–	–	0.2	–	–
Calarene	0.3	–	–	–	0.2
Longifolene	0.1	–	–	0.5	0.2
β-Caryophyllene	57.5	60.2	29.8	19.7	40.9
α-Bergamotene	2.6	6.4	0.2	2.1	4.1
α-Guaiene	–	–	–	–	–
β-Sesquiphellandrene	0.1	–	–	0.8	0.3
Aromadendrene	0.2	0.6	–	1.7	–
α-Humulene	8.3	–	4.3	3.7	6.0
β-Farnesene	–	–	–	–	–
α-Curcumene	–	–	–	0.1	0.9
γ-Amorphene	1.9	2.7	–	0.9	2.2
α-Amorphene	–	0.5	4.5	–	–
Germacrene D	2.4	0.7	15.9	0.4	5.0
β-Selinene	–	–	0.2	–	–
Bicyclogermacrene	–	0.5	–	–	–
α-Aromadendrene	–	–	–	3.8	–
Germacrene B	1.0	–	–	3.6	1.9
α-Muurolene	–	0.5	3.2	–	–
α-Bisabolene, cis-	–	–	–	–	–
β-Bisabolene	0.3	1.1	–	2.8	0.8
γ-Cadinene	0.6	0.3	1.6	–	2.1
δ-Cadinene	1.7	1.9	5.0	7.2	2.6
α-Cadinene	0.2	–	–	0.1	0.1
α-Selinene	–	–	–	0.1	0.2
β-Vetivene	0.1	–	–	0.5	0.2
α-Caryophyllenol	0.7	–	–	0.1	–
Ledol	0.2	–	0.2	0.5	–
Multigenol	–	–	–	–	0.3
Caryophylenne oxide	0.5	0.2	0.3	1.5	2.4
Globulol	–	–	0.2	–	–
Viridiflorol	–	–	0.4	–	–
Guaiol	0.2	–	–	0.3	–
Cedrol	0.4	–	–	1.4	0.6
Cadalene	0.4	–	–	0.4	0.6
τ-Muurolol	–	0.1	–	–	–
α-Muurolol	–	–	1.6	–	–
δ-Cadinol	–	0.9	–	–	–
α-Cadinol	–	0.1	2.1	0.7	0.6
α-Bisabolene oxide	0.4	–	–	–	–
β-Bisabolol	0.1	–	–	8.2	0.4
(z)-α-Santalol	–	0.2	–	–	–
α-Bisabolol, epi	–	–	–	–	–
Acetoxy-caryophyllene	0.2	–	–	–	–
Diterpenes*					
Aromadendrane ⟨dehydro⟩	–	–	–	–	–
Hexadecanoic methyl ester	–	–	–	–	–
Kaur-16-ene	–	–	–	–	1.6
Methyl Eperuate	0.4	–	–	0.8	–
Linoleic acid methyl ester	–	–	–	–	–

Table 1. Continued.

Compounds	*Copaifera multijuga* Hayne [147]	*Copaifera multijuga* Hayne [137]	*Copaifera multijuga* Hayne [148]	*Copaifera cearensis* Huber ex Ducke [147]	*Copaifera reticulata* Ducke [147]
Methyl cativate	–	–	–	0.5	–
Kaur-16-en-18-oic acid methyl ester	–	–	–	–	3.9
Methyl copalate	6.2	–	–	2.1	2.4
Methyl kolavenate	–	–	–	0.5	3.4
Kauran-19-oic acid methyl ester	–	–	–	–	–
Copalic acid methyl ester	–	9.5	7.1	–	–
Methyl hardwickiate	–	–	–	6.2	2.3
Methyl pinifolate	0.2	–	–	–	–
Methyl clorechinate	–	–	–	11.3	0.1
Dimethyl clerod 3-en-15,18-dioate	–	–	–	0.1	–
Dimethyl agathate	2.1	–	–	–	1.5
Labd-8(20)-ene-15,18-dioic acid methyl ester	–	–	4.2	–	–
Methyl 3-methyl-5 (2,2,6-trimethyl-6-hydroxy-1-cyclohexyl)-pentanoate	–	–	–	2.1	–
3β-Hydroxy-Copalic acid	0.6	0.8	1.0	–	–
3β-Acetoxy-Copalic acid	3.4	1.0	1.0	–	1.4

Note: *Diterpenes compounds identified after derivatization reaction.

oil results. For example, ion exchange chromatography was applied to the fractionation of the *Copaifera multijuga*), in non-aqueous medium, for separation of basic or acidic fractions from copaiba oil as an important unit operation in preparative scale for commercial purposes. In that study an anionic macroporous resin was successfully used for separation of the acid fraction of *Copaifera multijuga*, rich in labdanic diterpenes [149].

Phytochemical studies of the seeds obtained from *Copaifera salikounda Heck.* detected the presence of coumarin-type compounds. In more recent studies with oil from the seeds of a Brazilian *Copaifera* coumarins (0.15%) it was also detected in addition to palmitic (24.9%), oleic (35.3%), linoleic (35.7%), araquidínico (1.1%) and behenic (3.0%) acids. Reinforcing, studies with seed oil from *C. langsdorfii* showed a coumarin (named umbelliferone) and 40% of xyloglucans oligosaccharides [152–154].

Barreto-Júnior et al. (2005), Leandro et al. (2012), Santos et al. (2013), Veiga-Júnior et al. (2005) have shown that specific phytoconstituents could be obtained by the chromatography approach such as ionic resins that can retain the carboxylic acids and elute the bioactive sesquiterpenes and sequentially diterpenic acids [149] and silica modified with KOH [80]. Silica modified with KOH was used to separate diterpenoic acids to analyze their biological activity. Antileishmanial activity of several diterpenes isolated from copaiba oil were analyzed and 3-hydroxy-copalic acid was observed to be highly bioactive [79]. Similarly, diterpenic acids from copaiba oils had their synergistic effect together with caryophyllene analyzed to Chagas Disease. The activity was observed in copalic acid, 3-hydroxy-copalic acid and caryophyllene, but also, it was potentialyzed 20 times when copalic acid was put together with caryophyllene [78]. Some copaiba oils such as *Copaifera cearensis* and *Copaifera langsdorfii* could present a high content of kaurenoic acid as it can naturally precipitate forming crystals. For this reason, this diterpene is the most studied substance from copaiba oils [52].

Many other studies have been performed in order to confirm copaiba oil pharmacological activity properties, and also to validate its widespread use. From that it is known that copaiba oleoresin is used in the cosmetics and perfume industries as an important raw material as fixer, with fresh and acres notes that combine well with traditional florals [155]. In addition along with its emollient property, antibacterial and anti-inflammatory effects, in the manufacture of soaps, creams and bath foams, shampoos, conditioners, creams, lotions and capillaries, to soften hair [90, 156, 157]. The copaiba oil is also used as drying agent in the varnish industry, replacing the linseed oil [155].

Various pharmacological applications of oleoresin of *Copaifera spp.* have been described such as anti-inflammatory [126, 158–161], healing [162], gastroprotective [163–165], antitumoral [166–168], antimicrobial and antibacterial [169–173], anti-helminthic [174–175], antitetanus, antiseptic, antiblenorrhagea, and analgesic [159, 160] as well as tripanomicide, cervicitis and leukorrhea activities [176].

Among the medicinal properties of copaiba oil, the most studied is the anti-inflammatory, and its mechanism was investigated. This activity was related to the inhibition of the NF-B nuclear translocation, and consequently of proinflammatory cytokines secretion [161]. In this study, the antipsoriatic effect after oral intake/topical application was also investigated. In a preliminary clinical trial three patients affected by chronic psoriasis, treated with oral intake or topical application of the copaiba oil, exhibited a significant improvement of the disease typical signs, e.g., erythema, skin thickness, and scaliness.

Basile et al. (1988) studied the activity of commercial copaiba oil using various models in mice. It was to check the inhibition of carrageenan-induced edema, induction of granulomatous tissue and decreased vascular permeability caused by intradermal histamine release, with lower toxicity of copaiba oil [158]. Martins and Silva (2010) found that the *in natura* application of copaiba oil was able to reduce

edema and ceased the resulting purulent exudate infectious process of skin wounds [177]. A copaiba oil (*Copaifera langsdorffii*) based ointment favors angiogenesis and accelerates the viability of random skin flaps in rats [178].

The analgesic and anti-inflammatory activity of *C. duckei* showed significant results when used via the topical route in the carrageenan-induced paw edema, granuloma and croton oil-induced dermatitis tests [159]. The antinociceptive activity of two Amazonian copaiba oils (*Copaifera multijuga* Hayne and *Copaifera reticulate* Ducke) administered by the oral route using peripheral (acetic acid-induced abdominal writhing and formalin), spinal (tail flick) and supra-spinal (hot plate) models were studied. The copaiba oils demonstrate peripheral and central antinociceptive effects, and have been indicated to treat algesic disorders. This research demonstrated copaiba oils without toxic effects [179].

In the experimental model involving acetic acid-induced colitis in rats, it was observed that kaurenoic acid, applied together with acetic acid, decreased the inflammatory cell infiltrate and edema of the intestinal mucosa, suggesting copaiba oil as an anti-inflammatory agent [180]. Paiva et al. (2004) analyzed the effect of *Copaifera langsdorffii* in acetic acid-induced colitis. It was observed that the reduction in colonic myeloperoxidase, the marker of neutrophilic infiltration, and by a marked decrease in malondialdehyde level, has been an indicator of lipoperoxidation. The obtained results indicate the protective effect of copaiba oil in the animal model of acute colitis possibly through an antioxidant or an antilipoperoxidative mechanism [181]. The antiulcer activity of *C. langsdorffii* has been also reported [163–181].

The effects of copaiba oil on intestinal damage associated with mesenteric ischemia/reperfusion in rats proved a protective action against I/R-induced intestinal tissue damage and was correlated to the anti-oxidant and antilipid peroxidation properties [165]. The effects of *Copaifera langsdorffii* on ethanol, indomethacin and hypothermic restraint stress-induced gastric lesions were studied in rats. Results presented a gastroprotective potential of copaiba oil [163].

The effect of copaiba oil in correction of abdominal wall defects treated with polypropylene/polyglecaprone meshes in rats was analyzed. The copaiba oil reduced the amount of abdominal adhesions and accelerated the formation of collagen fibers without damaging the early stages of healing [182]. The effect of copaiba oil in rats with endometriosis was evaluated and a marked reduction in endometrial growth was observed [183]. The anti-inflammatory effect of copaiba oil on experimental acute pancreatitis induced by cerulein in mice was studied [184].

Copaiba oil administered prophylactically for seven days and therapeutically two hours after the acetaminophen acute intoxication offered a potential hepato protection against paracetamol-induced hepatic damage normalizing the biochemical parameters similarly to N-Acetyl-Cysteine, and the treatment with corn oil shows no effect on the liver damage [185, 186].

Lima et al. (2003) demonstrate that *C. multijuga* presents tumoricide activity in melanoma cells, both *in vitro* and *in vivo* experiments [167]. The possible protector effects of copaiba oil on the model of teratogenesis induced by cyclophosphamide in mice have been investigated. Copaiba oil presented a protective effect against teratogenesis induced by cyclophosphamide in the following skeletal structures: meta carpals, forepaws proximal phalanges, and tail vertebras. It also reduced the hydrocephalus frequency [168].

C. multijuga and its fractions demonstrated antineoplasic properties against Ehrlich ascitic tumor and solid tumor even after oral administration [187]. Chicaro (2009) demonstrated possible antitumor activity of copaiba oil due to inhibition of cell growth by induction of apoptosis and inhibition of cellular proliferation. Additionally, this oil decreased the NFkB protein expression, responsible for the regulation of genes involved in cell growth and suppression of apoptosis [188]. The cytotoxic effect of copaiba oil-based root canal sealer on osteoblast type Osteo1 cells has been evaluated. This oil presented promising results in terms of cytotoxicity which indicated its usefulness as a root canal sealer [189].

Brito et al. (2005) evaluated the levels of urea and creatinine in rats subjected to ischemia and reperfusion syndrome and observed that the prior administration of copaiba oil by gavage for seven days led to lower levels of metabolites in the urine, suggesting decreased vascular permeability to pro-inflammatory substances and reduction of cytotoxic agents in the renal parenchyma [190].

Santos et al. (2008) tested the antimicrobial activity of the genus *Copaifera*. The species *C. Martii, C. officinalis* and *C. reticulata* exhibited good antibacterial activity against gram-positive bacteria, including Methicillin-Resistant *Staphylococcus aureus* strains. The copaiba oils tested were inactive against gram-negative bacteria and the antifungal activity in the species *C. paupera* and *C. lucens, C. cearensis, C. langsdorffi* and *C. multijuga* proved to be moderate [172].

Santos et al. (2013) also evaluated the antibacterial activity of *Copaifera duckei* and determined its possible mechanism of action against bacteria. The results showed activity against 9 of the 11 strains of the tested bacteria in which *Bacillus cereus* was the most sensitive. *Copaifera duckei* oil-resin acted on the bacterial cell wall, removing proteins and the S-layer, and interfering with the cell-division process. This activity was attributed to the action of terpenic compounds, among them bisabolene [173].

Copaiba oil from *C. duckei* Dwyer also showed antimicrobial activity against strains *Candida albicans, Cryptococcus neoformans, Saccharomyces cerevisiae, Bacillus cereus, Enterococcus faecalis, Bacillus subtilis, Streptococcus pyogenes, Streptococcus salivarius* and *Micrococcus luteus.* This oil also presented bacteriostatic and bactericidal selective activity against gram-positive and fungi microorganisms in different concentrations [191].

The inhibitory activity of *Copaifera officinalis* against the *Streptococcus mutans* was evaluated and bacteriostatic activity was observed at copaiba oil low concentrations, and could be an option of phytotherapic agent to be used against cariogenic bacteria in the prevention of caries disease [192].

Several studies have shown that the use of copaiba oil has antileishmanial activity. Copaiba oils obtained from different species showed activity against promastigote forms of *Leishmania amazonensis* [193]. Significant antileishmanial activity of copaiba oil from *Copaifera reticulata* was demonstrated against axenic amastigote and intracellular

amastigote forms of the parasite. Additionally, the study demonstrated that copaiba oil oral treatment caused a significant reduction in the average lesion size in mice [194]. The morphological and ultrastructural changes in *L. amazonensis* treated with copaiba oil from *C. reticulata* were investigated in order to determine the specific organelles affected for copaiba oil [195]. Soares et al. has studied the effect of *trans*-caryophyllene as an effective antileishmanial compound [196]. The hydroalcoholic extract of *C. langsdorffii* leaves showed leishmanicidal and antimalarial activities [197] and was bioactive in animal models of urolithiasis [198] and nephrolithiasis [199].

The acaricidal activity of oilresin extract obtained from *Copaifera reticulata* was investigated against *Rhipicephalus (Boophilus)* microplus larvae [200]. The anti-helminthic [174, 175], trypanocidal [201, 202], anti-*Schistosoma mansoni* [175] and cercaricide [203, 204] effects of copaiba oil were comproved.

Figure 8 highlights by the geographical location of countries; studies developed with copaiba oil aiming at healthcare including biotechnological innovations. In this context, emulsion, nanoemulsio and microemulsion systems containing copaiba oil have been developed as promising vehicles for topical delivery of drugs. This topical subject will be discussed herein.

Concerning copaiba oil toxicity, a single dose of a volatile or resinous fractions obtained from this oil was 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 [134]. In another 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, induced behavioral alterations, or caused lesions or bleeding in the stomach of treated mice [147, 179]. The *C. langsdorffii* extract significantly reduced the extent of DNA damage and ACF induced by DMH, suggesting that the extract has a protective effect against colon carcinogenesis [205].

According to Sachetti et al. (2009), 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) [206]. It seems that copaiba oil for a reduced period with controlled doses is healthy. In large amounts or prolonged treatment periods it may cause side effects such as gastrointestinal irritation, nausea, vomiting, salivation, diarrhea and depression of the central nervous system. However, in the usual doses, it becomes a clinically safe agent.

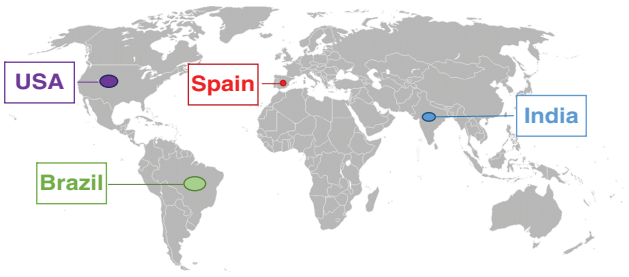

Figure 8. Geographical location of copaiba oil published studies applied to healthcare.

5. PATENTS FROM COPAIBA OIL AND FINAL COMMENTS FOR HEALTH BENEFITS ARISING FROM THE *COPAIFERA* SPECIES

Copaiba oil is obtained most of the time by extractive activities, being considered standard practice in Brazil, but that compromises the socioeconomic development of the country. Besides raising the risk of extinction of some plant species, to favor the realization of irregular collections, which do not respect the legal requirements and seasonal aspects, it was scientifically comproved that extractive activities results in changes in the *Copaifera* oil chemical composition due the great heterogeneity of the species. Therefore, this practice can compromise the therapeutic effectiveness, product acceptance and interest in the pharmaceutical industry [207].

The commercialized expansion of medicinal plants culminated in the misappropriation of biodiversity, making Brazil an ecologically vulnerable country. The growing devastation of ecosystems has led to a gradual and irreversible loss of species [208, 209]. According to the Brazilian agency monitoring the levels of habitat deforestation, destruction is rampant and only 50% of its natural cover remains. The Brazilian Cerrado region accounts for 30% of Brazil's biodiversity, and unfortunately a very small amount of its surface has been protected [210].

The preservation of biodiversity is of paramount importance and can be seen as a way to sustain life on the planet [211]. Taking into consideration the importance of plant species for humanity, studies for management, bioprospecting and conservation of the biodiversity are thoroughly carried out. 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 the right to preservation and rational use of biodiversity [212–215].

The preservation of the Brazilian plant diversity because of the numerous therapeutic properties has been considered as an alternative to generate innovative processes and products. This enormous biodiversity involves potential niche markets wherein the country can recover international competitiveness levels, while contributing to the improvement of people's quality of life, development of autonomous technologies and, on the whole, to national sovereignty. Therefore, the organized and properly performed appropriation of the biodiversity for industrial purposes is a powerful instrument for sustainable development [215–217].

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 industrialized countries come directly or indirectly from natural products [218]. Therefore, countries with high biodiversity have the opportunity to go into billion dollar markets

such as pharmaceuticals (which handles about 320 billion/year) and dietary supplements (which handles about 31 billion/year) [219–221].

In this context, encouraging the use of natural resources guided by WHO, it has stimulated the economies of the developing countries and increased applications for pharmaceuticals and cosmetics patents arising out of the local biodiversity [213, 222, 223]. Patenting 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 an individual or entity, regulating and promoting the technological innovation process. In fact, the current model of the international intellectual property system favors patent holders, and encourages scientific production and technological innovation. Thus, the analysis of the patent documents is one strategy for monitoring changes and advancements in technology, enabling identification of technological innovation trends over the years [224–226].

It is expected that in 2015, Brazil will have the fifth largest 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 [227]. Patent documents represent a valuable source of scientific information and the most popular search sites are the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO) and in Brazil, the National Institute of Industrial Property (INPI) [228].

Taking into account the number of patent requests for copaiba oil, Figure 9 shows the patents requested in class A61 (one human needs and 61 hygiene and medical clinic or veterinary) were found at INPI, EPO, USPTO and the World Intellectual Property Organization (WIPO) resource. From this, 21 documents belonged to Brazil, 9 Japan, 7 the United States, 3 Spain and 10 for other countries. However, when considering the use of copaiba in the last 20 years based on the information in patents, they found 17 documents and of these, fourteen were required by Japanese companies and only one was Brazilian [229]. On the other hand, the growth in the number of Brazilian patents highlights the interest in herbal markets and it could improve national biotechnology management.

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 and traditional knowledge [213].

The Convention on Biological Diversity is considered one of the most important international instruments related to protection of biodiversity and traditional knowledge. In this international agreement of the United Nations, the sovereign rights of states over their natural resources are recognized, ensuring conservation of biodiversity, sustainable use and the fair and equitable sharing of benefits arising from the utilization of genetic resources [212].

The Nagoya Protocol also contributed to inhibit biopiracy, establishing that for use of biodiversity, prior consent of the country or the local community would be needed, and division of the economic benefits generated from herbal marketing, economic development, preservation and sustainable use of natural resources must be observed [213].

In Brazil, the actions against the misappropriation of biodiversity are supported by a series of legislative, administrative and policy (Decree No. 2186-16), regulating the protection and access to genetic resources and traditional knowledge, benefit sharing and access to technology development [212, 225]. The biodiversity access is granted by the Board of Management of Genetic Heritage from a document that states the biological material that will be collected and the day, time, location, the fate of this biological material and the researcher who will perform the procedure [223]. Combatting biopiracy inhibits illegal trade of natural resources and the country could further the upward momentum of valuing the Brazilian biodiversity [230]. The WHO's current recommendation is that the leaders of each country update and record the traditional knowledge of its population, including the users' identification, herbal preparation form and health indications [222].

In the global context, Figure 10 shows the number of *Copaifera* species patent requests and Figure 11 highlights the statistic enhancement of the published studies with *in natura* copaiba oil. By analysis of the total copaiba oil patents ($n = 50$), 20 of these were recorded in EPO and 30 in the USPTO. The number of applications in the USPTO was higher than the EPO. Pointing to the growth in recent decades, those statistics can still be considered small in

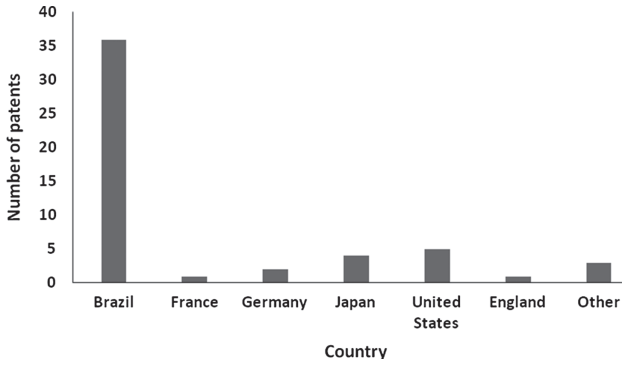

Figure 9. Number of patents per country requested in the period of 1950 to 2015 for copaiba oilresin aiming at health applications.

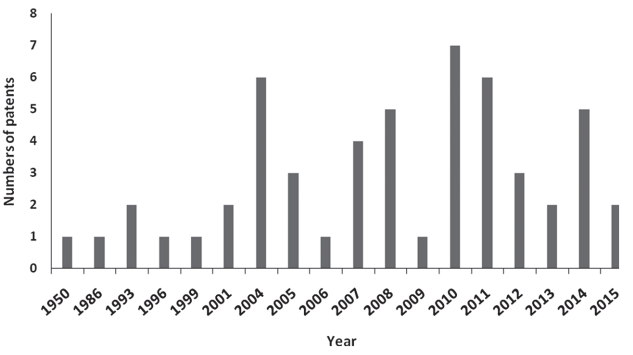

Figure 10. Annual worldwide growth number of copaiba oil patent requests.

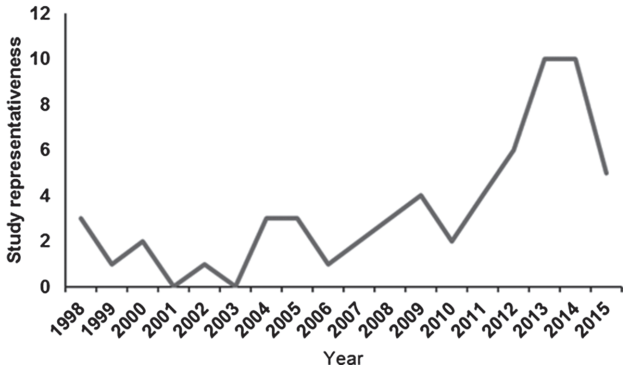

Figure 11. Enhancement of the published studies with *in natura* copaiba oil.

the face of the large medicinal availability of the *Copaifera* species.

The growth in the number of patents in recent years can been associated with enhancement and expansion of the natural products marketing in the local and international market, expanding the need for intellectual property protection, new studies and investment in the industrial sector [222, 223, 231, 332]. However, this growth remains limited in the number of Brazilian patents in the health area, reflecting the lack of resources for the development of products with *Copaifera* and the need for adjustments in the aspects involving public health policies and management of investments in social and economic issues [222]. Thus, the contrast is clear between the impressive economic growth potential arising from the use of biodiversity and the limited impact of the pharmaceutical industry in the Brazilian economy [207].

The current model of intellectual property protection began with a call from industry to gain control over the production of manufactured goods and subsequently to ensure mastery over the distribution and marketing of products, increasing the percentage of profit in industry. In the 19th century the right to industrial property shall be made by the patent registration. However, with the expansion of trade in the global context, there was the difficulty of controlling the negotiations by the absence or failure to comply with international rules, representing a new obstacle to maximizing profits in the industrial sector [225].

In the commercial context, to direct investments, the pharmaceutical companies analyzed the reasons for the use of traditional medicine, which differ among populations; and evaluated the market segment that is intended for production of the drug. The justification for the use of medicinal plants included limited access to conventional medicine; the historical and cultural influences; and the interest in a complementary therapy. In addition to these factors, the prevention of diseases, dissatisfaction with health services, adverse effects of drugs and the possibility of access to a different therapeutic alternative, less costly and more wide, are also recognized as other reasons that encourage people to seek alternative treatments [214, 231–233].

The annual reports of the National Institutes of Health, USA, emphasized that investment in new drug research and determination of benefits to public health, contribute to maintaining the pharmaceutical industry of the country in a leading position worldwide [234]. According to the Organization for Economic Cooperation and Development [135], the USA led the participation in pharmaceutical patent applications (38.6%) during the period between 2009 and 2011. However, Brazil ranks last in this ranking with 0.5% of patents, highlighting the need for investment in research and technological development.

Despite the appreciation of copaiba oil and evidence of its medicinal properties, a difficulty encountered in marketing and that may have impacted the growth of the number of patents is the wide variation in their chemical composition, within and between species [52, 235, 236]. Another limiting factor for use of medicinal plants by the industry is the collection dependent on the extractive activities which can compromise the quality required and the availability of raw materials for the manufacture of herbal medicines. Thus, the possibility of adulteration is very high, because many of these preparations do not have a quality certificate and were not subjected to preclinical and clinical studies to prove their effectiveness and safety [79, 207, 237, 238].

Since *Copaifera* was added to the list of 71 medicinal plants from the Brazil Health Ministry through the National Program of Medicinal Plants and Herbal medicines a significant expansion in the marketing and exploitation of the Brazilian copaiba oil is expected. In addition, *Copaifera* was presented as one of the plants with the potential to generate products of interest to the National Health System (National List of Medicinal Plants of Interest to Unique Health System—RENISUS); which may increase the number of scientific studies and biotechnological development [239].

Regarding patents involving copaiba oil, the oldest one is from 1898 (GB189803261) in which copaiba capsules were used in the treatment of inflammation in the urethra (gonorrhea) [240]. One of the many companies using this oil is the Technico-flor S/A that obtained a patent registration (FR2692480) in France in December 1993 for a "new cosmetic or food compositions including copaiba" [241]. In June 1994 the same record was achieved at WIPO (WO9400105) expanding it to patent world domination [242]. In the United States, the Aveda Corp achieved a patent registration (US5888251) in March 1999 for a "Method of coloring hair or eyelashes with compositions which contain metal containing pigments and a copaiba resin" [243]. 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 [223].

The number of patents containing copaiba oil for therapeutic purposes or cosmetics use has increased [244–249]. Kenupp et al. developed a patent process to preparations of copaiba oil extracts, fractions and isolated compounds from the *Copaifera* species for treatment of urinary lithiasis in human beings and animals [250]. In dentistry, an orthodontic cement containing *Copaifera multijuga* oil, a developed product, was subjected to laboratory analysis of its chemical and physical properties compared to three other commercial products. The results revealed that the experimental cement complies satisfactorily with the standards of the American Dental Association [251]. Simões et al. has developed a gel

containing copaiba oil for a dental application [252]. A considerable number of other therapeutic applications can still be found in the current literature [253–258]. From that, the market trend toward increased investment in copaiba oil biotechnology is 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 dispersed systems (e.g., emulsion, nanoemulsions, microemulsion, nanocapsules) with copaiba oil has been seen as a promising strategy, since they allow the delivery, topically, insoluble in water molecules, enhancing, including its therapeutic effect [148].

In this context, nanoemulsion has an important place in the pharmaceutical industry as a drug delivery system that increases the bioavailability of a large quantity of chemical substances which are lipophilic and have low aqueous solubility. Additionally, the nanometric size of these therapeutic formulations favors absorption of the drug, increase drug effects and decrease toxicity [259–261]. With the increasing application of natural products in the development of pharmaceutical formulations, patents have been published dealing with copaiba oil incorporation into a nanoemulsion for application to the skin wound healing process [262]. Another patent is the preparation and evaluation bioformulation containing copaiba oil for treating skin diseases through development of microemulsion systems [263]. In another study, copaiba oil was loaded in low concentration into a self-microemulsifying colloidal drug delivery system (SMEDDS) for a dental therapeutic application [264]. The process for obtaining microparticles from *Copaifera langsdorffii* with antilithiatic (kidney stones), analgesic, antispasmodic, anti-inflammatory, diuretic and antiseptic activity was also patented [265].

Recently Xavier-Junior et al. has developed an emulsion system containing copaiba oil as a promising vehicle for topical delivery of drugs and active cosmetic ingredients. The hydrophilic-lipophilic balance value of copaiba oil was 14.8; an emulsion system that has been stable for more than one year, and the pseudo-ternary diagrams were useful to describe the component proportions [266]. Earlier, Pontes et al. developed the dermatological emulsions containing copaiba oil [103].

Alencar et al. has developed nanostructured emulsions based on copaiba (*Copaifera langsdorffii*) resin-oil and copaiba essential oil against fungi and bacteria related to skin diseases. Given the significant antimicrobial and antibiofilm activities of the evaluated oils, it may be concluded that nanostructured emulsions based on copaiba oils are promising candidates for the treatment of infections, and also may be used to incorporate other antimicrobial drugs [171].

Recently, a nanoemulsion formulation containing copaiba oil was developed; the skin permeation/retention was evaluated [267] and nanoemulsions with reduced loss of volatile fraction within 90 days of storage was produced by the high-pressure homogenization method. In that study the use of medium-chain triglycerides was shown to be a good strategy to fix volatile fractions of copaiba oil incorporated into nanoemulsions during preparation and storage [268]. Before that, nanoemulsions as a delivery system for copaiba oil in view to treat locally inflamed skin was developed [148].

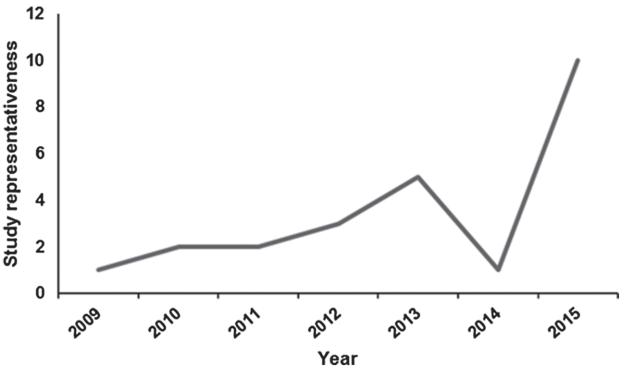

Figure 12. Representativity of biotechnology studies with copaiba oil aiming at healthcare.

Figures 12 and 13 show, respectively, the growth of biotechnology studies developed with copaiba oil to be applied as fitomedicine and the copaiba oil formulations type.

Recently, antibacterial properties of the natural oil from *Copaifera multijuga* which was embedded in biobased materials has been studied against grampositive bacteria (*Bacillus subtilis*). The author found that the copaiba oil incorporated on paper sheets and plastic films maintained the effective antibacterial properties, which can be used as biodegradable packaging with bactericide effect, to improve the shelf life of food products [269]. Oil-in-water nanoemulsions using copaiba oleoresin dispersed through a high internal phase was developed to potential insecticidal action against *Aedes aegypti* larvae. The low-cost ecofriendly green natural-based nanoformulations as a promising insecticidal agent with potential larvicidal activity was efficiently developed [270].

The copaiba oil world investment aiming at technological development for Brazilian public health enabled a large medicinal availability. In fact, from Table 2 it is possible to realize that copaiba oil represents an important raw material for the manufacture of herbal medicines, including its immunomodulatory, neuroprotective and anticâncer effects, hepatic damage and acute pancreatitis attenuation, suppresses inflammatory cytokines, influences ventral hernia repair, acts as an antileishmanial agent, among other medicinal properties. Additionally, other Brazilian *Copaifera* plant parts have been investigated as shown in Figures 14 and 15, as well as in Table 3. In that, phytomemistry and pharmacological studies were conducted. As a complement

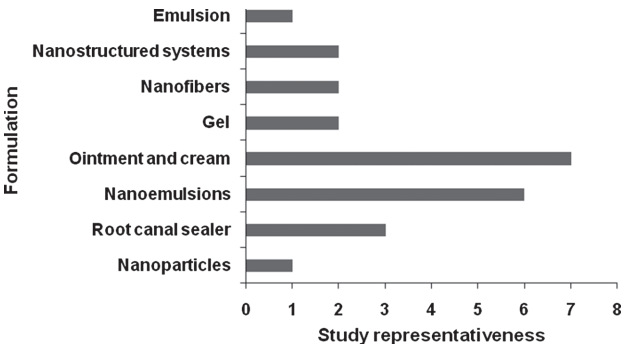

Figure 13. Copaiba oil based on different bioformulations.

Table 2. Studies developed with *in natura* copaiba oil applied in healthcare.

Purpose of the study	Pharmacological activity	Reference
Analyzed copaiba oil influence in the repair of abdominal defects in mice corrected with vicryl® mesh	Anti-inflammatory	[272]
Analyzed copaiba oil effect on bone regeneration of jaw defect in Wistar rats treated with bioglass or adipose tissue	Bone regeneration	[273]
Evaluation of the effects of copaiba oil as a prophylactic on survival of rats subjected to cecal ligation and puncture	Antimicrobial	[274]
Characterization of different copaiba oils and study their action in human monocytes	Immunomodulator	[275]
Evaluation of the *in vitro* influence of copaiba oil and other essential oils at different stages of the biological cycle of the tick Rhipicephalus microplus	Ovicides and acaricides	[276]
Investigation of the copaiba oil effects on liver injury induced by acetaminophen	Hepatoprotective	[185]
Evaluation effectiveness of *Copaifera officinalis* oil on inhibiting adhesion of *Candida albicans* biofilm	Antifungal	[277]
Evaluation of the copaiba oil effects as bioagent for pleurodesis induction	–	[278]
Evaluation of copaiba oil effects in the treatment of mice infected with *Trypanosoma evansi*	Trypanocide	[208]
Copaiba oil for oral treatment on reproductive performance of male Wistar rats	–	[279]
Investigation of the antioxidant and anti-inflammation activities of copaiba oil	Antioxidant and anti-inflammatory	[280]
Evaluation of the effects of copaiba oil administered by different routes on the survival of mice subjected to sepsis	Antimicrobial	[281]
Copaiba oil anti-inflammatory valuation performed using a model of acute pancreatitis induced by caerulein in rats	Anti-inflammatory	[184]
Pharmacological copaiba oil assessed using models of nociception in mice	Antinociceptive	[282]
Investigation of the copaiba oil immunomodulatory effects	Immunomodulator	[283]
Investigation of the antifungal activity of the copaiba oil against *Microsporum and Trichophyton* strains	Antifungical	[284]
Evaluation of the activity of the copaiba oil on gastric emptying	Antidopaminergic	[285]
Analyze of the immune response of copaiba oil in the treatment of walker 256 tumor	Anticancer	[286]
Analyze of the antiparasitic activity against *Trypanosoma cruzi*	Trypanocide	[287]
Investigated the leishmanicidal activity of four commercial oils from *Copaifera* spp. against *Leishmania amazonensis*	Leishmanicidal	[288]
Topical and systemic administration of copaiba oil in the alveolar healing after tooth extraction procedure	Bone regeneration	[289]
Analyzed the healing effect of copaiba oil on correction of abdominal wall defect	Tissue healing	[182]
Evaluated the *in vitro* antimicrobial activity of *Copaifera langsdorffii* oleoresin	Antimicrobial	[290]
Determined the phytochemical fingerprints of copaiba oils	–	[291]
To evaluate the anti-inflammatory and neuroprotective effects of copaiba oil in the tissues and preservation of the motor cortex	Neuroprotective	[292]
Investigated the morphological and ultrastructural changes in *L. amazonensis* treated with copaiba oil	Leishmanicidal	[195]
Inhibitory activity of Copaiba oil (*Copaifera officinalis*) against cariogenic microorganisms, *Streptococcus mutans*	Antimicrobial	[192]
Genotoxicity assessment of Copaiba oil	–	[293]
Neuroprotective and anti-inflammatory effects of oleoresin copaiba after neural disorders	Neuroprotective	[294]
Investigate copaiba oil efficiency as larvicide in wild populations of *Aedes aegypti*	Larvicide	[295]
Evaluation of the larvicidal activity and the residual effect of copaiba and andiroba oils against *Aedes aegypti*	Insect repellent	[296]
Evaluated the effects of oral treatment with copaiba oil in Leishmania injuries	Leishmanicidal	[194]
Anti-inflammatory effect and activity under central nervous system	Anti-inflammatory and neuroprotective	[235]
Developmental toxicity of copaiba oil	–	[206]
Changes in the volume and histology of endometriosis foci in rats treated with copaiba oil	Treatment of endometriosis	[297]
Mechanical resistance of the digestive tract after intestinal anastomotic surgery	Intestinal healing	[298]
Effect of copaiba balsam on walker 256 carcinoma inoculated into the vagina and uterine cervix of female rats	Anticancer	[299]
Antifungal effects of copaiba oil against five species of fungi	Antifungical	[300]
Effect of copaiba oil on ischemia-reperfusion of randomized skin flaps in rats	Healing	[124]
Investigation of anxiolytic acute effect	Anxiolytic	[301]
Evaluation of *C. langsdorffii* in the process of skin healing and induced inflammation	Healing	[302]
Antineoplasic activity of *Copaiba* oil against ascitic and solid Ehrlich tumor	Anticancer	[187]
Leishmanicidal activity of eight different types of Brazilian copaiba oil	Leishmanicidal	[193]
Anti-inflammatory and skin healing of *C. langsdorffii*	Anti-inflammatory and skin healing	[303]
Investigation of chemical composition and anti-inflammatory activity of various samples of copaiba oil	Anti-inflammatory	[147]

Table 2. Continued.

Purpose of the study	Pharmacological activity	Reference
Antinociceptive activity of copaiba oil	Antinociceptive	[179]
GC analysis of several samples of copaiba oils	–	[304]
Effect on aminotransferases of rats with hepatic ischemia and reperfusion	–	[101]
Evaluation of copaiba oil effects on edema and granuloma induced by carrageenan	Anti-inflammatory and analgesic	[159]
Copaiba oil effect on urea and creatinine serum levels in rats submitted to kidney ischemia and reperfusion syndrome	Anti-inflammatory	[190]
Protective effect of *Copaifera langsdorffii* oleoresin against acetic acid induced colitis in rats	Gastroprotective	[163, 181]
Antiproliferative activity of *Copaifera duckei* oleoresin on liver regeneration in rats	Healing liver	[305]
Attenuation of ischemia/reperfusion-induced intestinal injury by oleoresin from *Copaifera langsdorffii* in rats	Anti-inflammatory	[165]
Uterine cervix morphological and morphometric aspects of rats after application of copaiba oil	–	[306]
Characterization of the chemical composition of oleoresins of *Copaifera guianensis* Desf., *Copaifera duckei* Dwyer and *Copaifera multijuga* Hayne	–	[307]
Investigation on the wound healing activity of copaiba oleoresin	Healing	[125, 162, 308]
Anti-inflammatory activity of oleoresin from Brazilian *Copaifera*	Anti-inflammatory	[158]

of those data and specific comments some copaiba review articles could be accessed [3, 52, 90, 141, 147].

Polyphenols were obtained from fruit, sesquiterpenes were isolated from leaves (α-copaene, α-bergamotene, β-caryophyllene, α-humulene, caryophyllene oxide, bicyclogermacrene, germacrene D, germacrene B, δ-cadinene and α-cadinol), and flavonoids (quercitrin and afzelin). Sesquiterpenes were also obtained from stems and roots. The seed oil presents a characteristic odor of coumarin compounds and the fatty acid composition (linoleic acid, monounsaturated, and saturated fat), and for the lipid-free seeds (carbohydrate and protein). The presence of coumarin and xyloglucan as major components of *C. langsdorfii* seeds denotes its potential for use in the cosmetic or pharmaceutical industries [271].

Concerning the studies developed with chemical constituents isolated from copaiba oil aimed at healthcare it was found that among cytotoxicity, genotoxicity, chemotherapy, antileishmanial, antimicrobial, antiparasitic, antipsoriatic and anti-inflammatory investigations (Table 4), the greatest number was from the Brazilian *Copaifera* species.

For antimicrobial activity evaluation: (a) solid lipid nanoparticles containing copaiba oil were developed and evaluated on antifungal activity; (b) chemical characterization of natural oil nanostructured emulsions and the antimicrobial activity of nanostructured Amazonian oils against *Paenibacillus* species (and also their toxicity) on larvae and adult worker bees; (c) a solution blow spun poly(lactic acid)/polyvinylpyrrolidone nanofibers loaded with copaiba oil (*Copaifera* sp.) for *in vitro* antimicrobial propose. Additionally, (d) synergistic enhancement of parasiticidal activity of amphotericin B using copaiba oil in a nanoemulsified carrier was applied for oral delivery aiming at non-toxic chemotherapy study; (e) a co-encapsulation of imiquimod and copaiba oil in novel nanostructured systems tested against skin carcinoma; (f) using a novel HS-GC/MS method it determined the β-caryophyllene skin permeation/retention from crude copaiba oil (*Copaifera multijuga* Hayne) and respective oil-based nanoemulsion; (g) different methods optimized copaiba oil-based nanoemulsions aimed at medical applications, among other important researches (Table 5).

Finally it is important to reinforce that the oldest chemical study with copaiba oleoresin dates back to the beginning of the 19th century, when Schweitzer, in 1829, described how copaivic acid was identified from the left standing copaiba oleoresin, that turned into a solid substance and crystallized as copaivic acid [90]. Characteristically, copaiba oleoresin has a unique chemical composition composed by a solid fraction, non-volatile resinous (formed by diterpenic acids

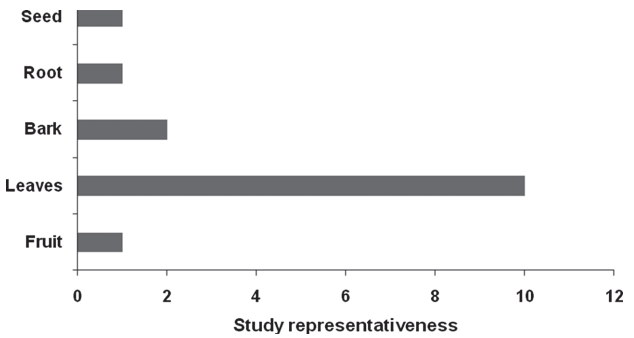

Figure 14. Representativity phytomemistry and pharmacology investigations for different *Copaifera* plant parts.

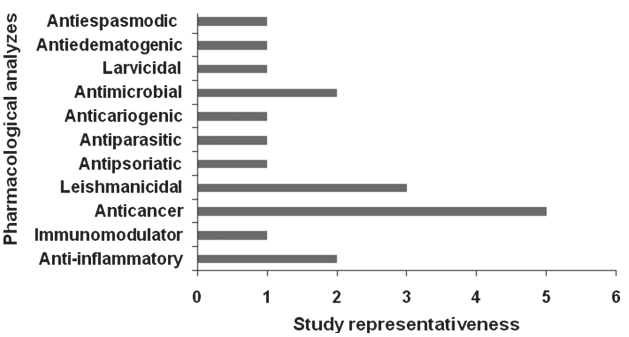

Figure 15. Pharmacological representativity of the whole *Copaifera* plant parts investigations.

Table 3. Phytomemistry and pharmacological studies developed with different *Copaifera* plant parts to be applied in healthcare.

Plant part	Pharmacological activity	Reference
Fruit	Antioxidant and antimutagenic	[309]
Leaves	Gastroprotective	[310, 311]
Leaves	Neuroprotective and anti-inflammatory	[312]
Leaves	–	[313]
Leaves	Antiedematogenic	[314]
Leaves	Anticancer	[205, 315]
Leaves	Antinephrolithiasis	[199]
Leaves	Antioxidant	[316]
Leaves	Anti-urolithiasis	[317]
Leaves, bark and root	–	[318]
Seed	–	[271]

corresponding 55% to 60% of the oil composition), and volatile fraction composed by sesquiterpenes [82, 90, 102, 110, 111, 115]. The copalic acid is used as a biomarker to copaiba oil, since it was found in all copaiba oils analyzed by gas chromatography [80, 90]. On the other hand, caryophyllene oxide, kaurenoic acid, and β-caryophyllene are reported as the major compounds found in copaiba oil [198]. The constitution of sesquiterpenes and diterpenes already received several published reviews. The sesquiterpenes are typically hydrocarbons, and sometimes their oxygenated derivatives, such as caryophyllene oxide and cadinol. The diterpenes belong to three skeletons: labdane, clerodane and kaurane, and are mainly carboxylic acids, with some exceptions, such as labdadienol and kaurene. Copaiba oils are sometimes described as a diterpenic resin solubilized on a sesquiterpene-rich essential oil [3, 80, 52, 90].

In a general context, the Brazilian environmental folk medicine culture has been stronger in the Amazon region, where according to Prance (1992), Van Den Berg correlated 1,200 different medicinal plants in the street market called "Ver-o-peso" in Belém, the state capital of Pará [3]. This market is part of the centuries-old folk medicine culture of Belém. Other 260 species, originally natives or cultivated, were found in two communities of Marajó (Pará) [3]. In addition, 242 cultivated species were catalogued in home

Table 4. Studies with the constituent isolated from copaiba oil applied in healthcare.

Purpose of the study	Pharmacological activity	Country	Reference
In vitro cytotoxicity and anti-inflammatory effects of 6 diterpene acids: copalic, 3-hydroxy-copalic, 3-acetoxy-copalic, hardwickiic, kolavic-15-metyl ester, andkaurenoic, isolated from the oleoresins of *Copaifera* spp	Anti-inflammatory	Brazil	[319]
Analysis of β-caryophyllene and β-caryophyllene oxide bioavailabilities and its absorption through cell membranes	–	Brazil	[320]
Systemic immunomodulation potential of *trans*-caryophyllene as possible prophylactic agent of leukopenia secondary in chemotherapy	Immunomodulator	Brazil	[321]
Identify new small chaperone inhibitors from copaiba oil fractions (copalic acid, hardwickiic acid and 3-acetoxycopalic acid)	Anticancer	USA	[322]
Investigation of leishmanicidal activity of *trans*-β-caryophyllene	Antileishmanial	Brazil	[288]
GC-MS characterization of the volatile and non-volatile compounds from *Copaifera langsdorffii* Desf. and investigation of anti-inflammatory mechanism and antipsoriatic effect	Antipsoriatic	Brazil	[161]
Investigation of antileishmanial activity of diterpene acids as methyl copalate and agathic, hydroxycopalic, kaurenoic, pinifolic and polyaltic acids isolated from *Copaifera officinales* oleoresins	Antileishmanial	Brazil	[79]
Genotoxicity evaluation of copaiba oil and their volatile and resinous fractions	Anticancer	Brazil	[293]
Antiparasitic and synergic activity of terpenes (methyl copalate, copalic acid, 3β-hydroxycopalic acid, agathic acid, pinifolic acid, polyaltic acid, kaurenoic acid, and β-caryophylene) from *Copaifera*	Antiparasitic	Brazil	[78]
Investigation of anticariogenic activity of nine terpenes and four sesquiterpenes from *Copaifera langsdorffii* Desf.	Antimicrobial	Brazil	[150]
Evaluation of the antimicrobial activity of sclareol, manool, (−)-copalic acid, (−)-acetoxycopalic acid, (−)-hydroxycopalic acid, (−)-agathic acid isolated from *Copaifera langsdorffii* against periodontal anaerobic bacteria	Antimicrobial	Brazil	[323]
Evaluation of *Copaifera multijuga* fractions against ascitic and solid Ehrlich tumor	Anticancer	Brazil	[187]
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 *Copaifera reticulata* Ducke against Aedes aegypti (L.)	Larvicidal	Brazil	[324]
In vivo antiedematogenic activity of fractions from *Copaifera multijuga* Hayne	Antiedematogenic	Brazil	[325]
Genotoxicity evaluation of kaurenoic acid	Anticancer	Brazil	[104]
Relaxant effect of kaurenoic acid from *Copaifera langsdorffii* on uterus	Antispasmodic	Brazil	[326]
Inhibition of lung metastasis and tumor growth induced by melanoma cells using fractions from *Copaifera multijuga* Hayne	Anticancer	Brazil	[167]
Leishmanicidal, antimicrobial, cytotoxic activities and inhibitory aldose reductase of various constituents from *Copaifera paupera*	Antileishmanial and antimicrobial	Spain	[327]
Anti-inflammatory effect of kaurenoic acid from *Copaifera langsdorffi*	Anti-inflammatory	Brazil	[328]

Table 5. Biotechnology applied to copaiba oil studies.

Formulation	Pharmacological activity	Country	Reference
Solid lipid nanoparticles containing copaiba oil and allantoin	Antifungal	Brazil	[329]
Nanoemulsion containing copaiba oil and amphotericin B for oral delivery	Leishmanicidal	India	[330]
Nanofibers	Antimicrobial	Brazil	[331]
Nanostructured systems	Antineoplastic	Brazil	[332]
Nanoemulsion	Antimicrobial	Brazil	[333]
Nanoemulsion	Cutaneousanti-Inflammatory	Brazil	[334]
Nanoemulsion	Antimicrobial	Brazil	[171]
Endodontics pastes	Antimicrobial	Brazil	[335]
Nanocomposite	Anti-endometriosis	Brazil	[267]
Vaginal cream	Antimicrobial	Brazil	[336]
Nanoemulsion	–	Brazil	[337]
Ointment	Healing	Brazil	[178]
Ointment	Cutaneous wound healing	Brazil	[338]
Electrospun nanofibers	Cutaneous wound healing	Brazil	[339]
Copaiba oil Cream	Cutaneous wound healing	Brazil	[340]
Ointment	Antimicrobial and cutaneous wound healing	Brazil	[341]
Emulsion	–	Brazil	[342]
Nanoemulsion	Cutaneousanti-Inflammatory	Brazil	[148]
Gel	Anti-acne	Brazil	[343]
Endodontics pastes	–	Brazil	[344]
Vaginal cream	Antimicrobial	Brazil	[345]
Dental gel	Antimicrobial	Brazil	[346]
Root canal sealer	–	Brazil	[251]
Ointment	Healing	Brazil	[347]

backyards [115]. In other regions of Brazil the use of extracts from Brazilian medicinal plants in the treatment of human disease is a common practice, which has increased greatly. Meanwhile, many vegetal extracts are used by people without knowledge of the side effects they can have upon their health. The Amazon Forest is well known for its great diversity of species of medicinal plants. In its Brazilian part, several of them have been used as medicine according to popular tradition, although, at present, there is still a lack of knowledge concerning their chemical composition [115]. This is not the case of copaiba oil, which has largely been used as medicine, and its pharmacologic and phytochemical analyses were widely developed aiming at its biotechnological improvement.

GLOSSARY

Biodiversity is a compound word derived from "biological diversity" and therefore is considered to have the same meaning*

Biological diversity means the variability among living organisms from all sources including, inter alia, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are a part; this includes diversity within species, between species and of ecosystems.*

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.

Emulsions is a mixture of two or more liquids that are normally immiscible.

Nanotechnology area of pharmaceutical sciences that study the development of drug delivery systems.

Patents is a set of exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention.

*Convention on Biological Diversity 1992.

REFERENCES

1. M. A. M. Maciel, T. N. C. Dantas, J. K. P. C. Cortez, A. C. Pinto, V. F. Veiga-Júnior, C. R. Kaiser, N. A. Pereira, C. M. T. S. Carneiro, F. A. Vanderline, A. J. Lapa, A. R. Agner, I. M. S. Cólus, J. E. Lima, A. E. Souza, K. Pissinate, and A. Echevarria, "Advances in Phytomedicine" (M. T. H. Khan and A. Ather, Eds.), p. 229, Elsevier, New York, NY, 2006.
2. M. A. M. Maciel, F. E. S. Gomes, B. A. Soares, N. F. Grynberg, A. Echevarria, I. M. S. Cólus, C. Kaiser, W. A. Morais, and N. S. S. Magalhães, "Bioactive Phytochemicals: Perspectives for Modern Medicine," p. 239, Daya Publishing House, Nova Delhi, 2014.
3. M. A. M. Maciel, A. C. Pinto, and V. F. Veiga-Júnior, *Quim. Nova* 25, 429 (2002).
4. WHO, "General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine," World Health Organization, Geneva, 2000.
5. J. C. Viegas, V. S. Bolzani, and E. J. Barreiro, *Quim. Nova* 29, 326 (2006).
6. M. G. Brandao, N. N. Zanetti, P. Oliveira, C. F. Grael, A. C. Santos, and R. L. Monte-Mor, *J. Ethnopharmacol.* 120, 141 (2008).
7. M. F. Agra, P. F. Freitas, and J. M. Barbosa-Filho, *Rev. Bras. Farmacogn.* 17, 1 (2007).
8. C. Desmarchelier, J. Coussio, and G. Ciccia, *Braz. J. Med. Biol.* 1163 (1998).
9. D. T. Rispler and J. Sara, *J. Am. Acad. Orthop. Surg.* 19, 634 (2011).
10. M. S. Tsuboy, J. C. Marcarini, R. C. Luiz, I. B. Barros, D. T. Ferreira, L. R. Ribeiro, and M. S. Mantovani, *J. Med. Food.* 13, 503 (2010).
11. L. F. Alves and P. F. P. Santos, *Rev. Bras. Farm.* 94, 307 (2013).
12. J. D. Vilela, *Rev. Paul. Med.* 89, 115 (1977).
13. J. R. Valle, "A Farmacologia no Brasil, Antecedentes e Perspectivas," Academia de Ciências do Estado de São Paulo, São Paulo, 1978.
14. G. M. Gragg and D. J. Newman, "Química de Produtos Naturais. Novos Fármacos e a Moderna Farmacognosia" (R. Yunes and V. Cechinel-Filho, Eds.), p. 51. Editora da Univali, Itajaí, 2012.
15. A. C. Pinto, D. H. S. Silva, V. S. Bolzani, N. P. Lopes, and R. A. Epifânio, *Quim. Nova* 25, 45 (2002).
16. L. C. Di Stasi, "Plantas medicinais: verdades e mentiras - O que os usuários e os profissionais de saúde precisam saber," UNESP, São Paulo, 2007.
17. J. K. Crellin, *Pharm. Hist.* 31, 43 (2001).
18. S. Balakumar, S. Rajan, T. Thirunalasundari, and S. Jeeva, *Asian Pac. J. Trop. Med.* 4, 654 (2011).

19. A. R. Bilia, C. Guccione, B. Isacchi, C. Righeschi, F. Firenzuoli, and M. C. Bergonzi, *Evid. Based. Complement. Alternat. Med.* 2014, 651593 (2014).
20. N. Chahlia, *J. Med. Plant. Res.* 3, 481 (2009).
21. S. Rajan, T. Thirunalasundari, and S. Jeeva, *Asian Pac. J. Trop. Med.* 4, 294 (2011).
22. D. M. Eisenberg, R. C. Kessler, C. Foster, F. E. Norlock, D. R. Calkins, and T. L. Delbanco, *N. Engl. J. Med.* 328, 246 (1993).
23. F. Firenzuoli and L. Gori, *Evid. Based. Complement. Alternat. Med.* 4, 37 (2007).
24. J. M. Ritter, *Br. J. Clin. Pharmacol.* 66, 418 (2008).
25. D. L. Moreira, S. S. Teixeira, M. H. D. Monteiro, A. C. A. X. Oliveira, and F. J. R. Paumgartten, *Rev. Bras. Farmacogn.* 24, 248 (2014).
26. M. D. Agra, K. N. Silva, I. J. L. D. Basílio, P. F. Freitas, and J. M. Barbosa, *Rev. Bras. Farmacogn.* 18, 472 (2008).
27. WHO, "Estrategia de la OMS sobre Medicina tradicional 2002–2005," World Health Organization, Genebra, 2002.
28. M. M. Cowan, *Clin. Microbiol. Rev.* 12, 564 (1999).
29. S. E. Cañigueral, A. L. Dellacassa, and A. L. Bandoni, *Lat. Am. J. Pharm.* 22, 265 (2003).
30. H. G. Bach, M. L. Wagner, R. A. Ricco, and R. H. Fortunato, *Rev. Bras. Farmacogn.* 24, 258 (2014).
31. P. Doyle, "Aspectos Técnicos, Culturales, Políticos y Legales de la Bioprospección en Argentina" (E. Y. Suares, Ed.), ICBG, Buenos Aires, 1999.
32. E. D. Almada, "Etnobiologia e Etnoecologia. Pessoas and Natureza na América Latina" (V. A. Silva, A. L. S. Almeida, and U. P. Albuquerque, Eds.), p. 39 NUPEEA, Recife, 2010.
33. R. Nair, T. Kalariya, and C. Sumitra, *J. Bot.* 29, 41 (2005).
34. D. Bown, "Royal Horticultural Society Encyclopedia of Herbs and their Uses." Dorling Kindersley, London, 2003.
35. U. P. de Albuquerque, J. M. Monteiro, M. A. Ramos, and E. L. de Amorim, *J. Ethnopharmacol.* 110, 76 (2007).
36. F. Leitao, S. G. Leitao, M. Z. Almeida, J. Cantos, T. Coelho, and P. E. Silva, *J. Ethnopharmacol.* 149, 513 (2013).
37. R. P. Borris, *J. Ethnopharmacol.* 51, 29 (1996).
38. D. E. Moerman, *J. Ethnopharmacol.* 52, 1 (1996).
39. D. D. Murphy, "Biodiversity" (E. O. Wilson and F. M. Peter, Eds.), p. 71, National Academy of Sciences/Smithsonian Institution, Washington, 1988.
40. A. R. R. Sandes and G. Di Blasi, *Biotecnolog.* 13, 28 (2000).
41. J. L. Harper and D. L. Hawksworth, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 345, 5 (1994).
42. A. P. Dobson, "Conservation and Biodiversity," Scientific American Library, New York, 1996.
43. B. F. S. Dias, "A implementação da convenção sobre diversidade biológica no brasil: desafios e oportunidades," Instituto de estudos avançados da Universidade de São Paulo, São Paulo, 2000.
44. P. J. P. Sant'ana and A. L. O. Assad, *Biotecnolog.* 29, 32 (2001).
45. M. Brandao, G. P. Cosenza, F. L. Pereira, A. S. Vasconcelos, and C. W. Fagg, *Environ. Monit. Assess.* 185, 7013 (2013).
46. A. P. Balbani, D. H. Silva, and J. C. Montovani, *Expert. Opin. Ther. Pat.* 19, 461 (2009).
47. T. A. Geissman, "Flavonoid Compounds, Tannins, Lignins and Related Compounds," Elsevier, New York, NY, 1963.
48. S. Sukumaran, S. Kiruba, M. Mahesh, S. R. Nisha, P. Z. Miller, C. P. Ben, and S. Jeeva, *Asian Pac. J. Trop. Med.* 4, 735 (2011).
49. I. H. Bassole and H. R. Juliani, *Molecules* 17, 3989 (2012).
50. H. Schäfer and M. Wink, *Biotechnol. J.* 4, 1684 (2009).
51. L. Martino, V. Feo, F. Fratianni, and F. Nazzaro, *Nat. Prod. Commun.* 4, 1741 (2009).
52. L. M. Leandro, S. Vargas F, P. C. Barbosa, J. K. Neves, J. A. Silva, and V. F. Veiga-Júnior, *Molecules* 17, 3866 (2012).
53. I. Rasooli, "Bioactive Compounds in Phytomedicine," InTech, Croatia, 2011.
54. Biodiversity in Brazil, "United Nations Conference on Biological Diversity (Cop11)," Hyderabad, India, 2012.
55. H. Ter Steege, N. Pitman, D. Sabatier, H. Castellanos, P. V. D. Hout, D. C. Daly, M. Silveira, O. Phillips, R. Vasquez, T. V. Andel, J. Duivenvoorden, A. A. Oliveira, R. Ek, R. Lilwah, R. Thomas, J. V. Essen, C. Baider, P. Maas, S. Mori, J. Terborgh, P. N. Vargas, H. Mogollón, and W. Morawetz, *Biodivers. Conserv.* 12, 2255 (2003).
56. W. J. Kress, W. R. Heyer, P. Acevedo, J. Coddington, D. Cole, T. L. Erwin, B. J. Meggers, M. Pogue, R. W. Thorington, R. P. Vari, M. J. Weitzman, and S. H. Weitzman, *Biodivers. Conserv.* 7, 1577 (1998).
57. M. C. Ribeiro, J. P. Metzger, A. C. Martensen, F. J. Ponzoni, and M. M. Hirota, *Biol. Conserv.* 142, 1144 (2009).
58. L. F. W. Roesch, F. C. B. Vieira, V. A. Pereira, A. L. Schünemann, I. F. Teixeira, A. J. T. Senna, and V. M. Stefenon, *Divers.* 1, 182 (2009).
59. A. Pott and V. J. Pott, "Plants of Pantanal," Embrapa, 1997.
60. J. B. Calixto, *Cienc. Cult.* 55, 1053 (2003).
61. G. M. Cragg, D. J. Newman, and K. M. Snader, *J. Nat. Prod.* 60, 52 (1997).
62. Y. Z. Shu, *J. Nat. Prod.* 61, 8 (1998).
63. B. Schmidt, D. M. Ribnicky, A. Poulev, S. Logendra, W. T. Cefalu, and I. Raskin, *Metabolism.* 57, S3 (2008).
64. G. M. Cragg and D. J. Newman, *Cancer. Invest.* 17, 153 (1999).
65. D. A. Oliveira, P. A. Moreira, A. F. Melo-Júnior, and M. A. S. Pimenta, *Unimontes Cient.* 8, 23 (2006).
66. R. Verpoorte, *Drug Discov. Today* 3, 232 (1998).
67. A. Odalia-Rímoli, E. J. Arruda, J. Rímoli, N. R. Bueno, and R. B. Costa, *Rev. Inter. Desenvolv. Local* 1, 21 (2000).
68. L. C. Oliveira and M. I. Bloise, *Cosmet. Toiletries* 7, 18 (1995).
69. P. A. Rocha-Filho, *Cosmet. Toiletries* 7 (1995).
70. B. H. Kroes, *J. Ethnopharmacol.* 158, 449 (2014).
71. BRASIL, "Guia de orientação para registro de medicamento fitoterápico e registro e notificação de produto tradicional fitoterápico," ANVISA, Brasilia, 2014.
72. O. Folashade, H. Omoregie, and P. Ochogu, *Int. J. Biodivers. Conserv.* 4, 101 (2012).
73. M. Raileanu, L. Todan, M. Voicescu, C. Ciuculescu, and M. Maganu, *Mater. Sci. Eng. C. Mater. Biol. Appl.* 33, 3281 (2013).
74. A. Angioni, A. Barra, V. Coroneo, S. Dessi, and P. Cabras, *J. Agric. Food. Chem.* 54, 4364 (2006).
75. Z. Q. Shi, D. F. Song, R. Q. Li, H. Yang, L. W. Qi, G. Z. Xin, D. Q. Wang, H. P. Song, J. Chen, H. Hao, and P. Li, *J. Chromatogr. A* 1345, 78 (2014).
76. N. Sahoo, P. Manchikanti, and S. Dey, *Fitoterapia* 81, 462 (2010).
77. S. Gafner and C. Bergeron, *Curr. Pharm. Anal.* 1, 203 (2005).
78. E. Izumi, T. Ueda-Nakamura, V. F. Veiga-Júnior, A. C. Pinto, and C. V. Nakamura, *J. Med. Chem.* 55, 2994 (2012).
79. A. O. Santos, E. Izumi, T. Ueda-Nakamura, B. P. Dias-Filho, V. F. Veiga-Júnior, and C. V. Nakamura, *Mem. Inst. Oswaldo Cruz.* 108, 59 (2013).
80. V. F. Veiga-Júnior, W. F. Braga, M. L. Patitucci, O. A. C. Antunes, L. Bergter, F. M. S. Garrido, and A. C. Pinto, *J. Braz. Chem. Soc.* 11, 355 (2000).
81. W. H. Lewis, "Medical Botany: Plants Affecting Human Health," John Wiley and Sons, New York, 2003.
82. V. Cascon, "Fitoterápicos anti-inflamatórios: aspectos químicos, farmacológicos e aplicações terapêuticas," (J. C. T. Carvalho, Ed.), p. 480, Tecmedd, Ribeirão Preto, 2004.
83. R. M. Rodrigues, "A Flora da Amazônia," Editora Cejup, Belém, 1989.
84. J. Léry, "Histoire Dún Voyage Fait en la Terre du Brésil-1557" (F. Lestringant, Ed.), Max Chaleil, Paris, 1578.
85. "Grande Enciclopédia Larrousse Cultural," p. 1608, 1998.
86. C. F. P. Von-Martius, "Systema de Materia Medica Vegetal," Eduardo and Henrique Laemmert, Rio de Janeiro, 1854.

87. J. D. Hooker and B. D. Jackson, "Index Kewensis," Claredon Press, Oxford, 1996.
88. A. Burkart, "Las leguminosas Argentinas," Acme Agency, Buenos Aires 1943.
89. N. V. Gramosa, E. R. Silveira, B. C. Cavalcanti, J. R. Ferreira, F. S. Oliveira, V. S. Rao, L. V. Costa-Lotufo, M. O. Moraes, and C. Pessoa, "30 Drug Plants I" (A. S. Awaad, J. N. Govil, and V. K. Singh, Eds.), p. 235, Studium Press LLC, Houston, 2010.
90. V. F. Veiga-Júnior and A. C. Pinto, *Quim. Nova* 25, 273 (2002).
91. H. C. Wood, C. H. LaWall, H. W. Youngken, A. Osol, I. Griffith, and L. Gershenfeld, "The Dispensatory of the United States of America," J. B. Lippincott Company, London, 1940.
92. W. Mors and C. T. Rizzini, "Useful Plants of Brazil," Holden-Day Inc., San Francisco, 1966.
93. M. Pio Corrêa, "Dicionário das Plantas Úteis do Brasil," Ministério da Agricultura, Rio de Janeiro, 1931.
94. E. Perrot, "Matières premières usuelles du Règne vegetal" Masson and Cia Paris, 1994.
95. B. M. Lawrence, "Natural Flavor and Fragrance Materials: Chemistry, Analysis, and Production," (C. Frey and R. L. Rouseff, Eds.), p. 32, American Chemical Society, Oxford, 1988.
96. A. M. C. Leite and E. Lleras, *Acta Bot. Bras.* 7, 61 (1993).
97. J. D. Dwyer, *Brittonia* 7, 143 (1951).
98. J. Alencar, *Acta Amazon.* 12, 79 (1982).
99. H. Lorenzi, "Árvores brasileiras: manual de identificação e cultivo de plantas arbóreas nativas do brasil," Instituto Plantarum, Nova Odessa, 1992.
100. N. Xena and P. E. Berry, "Flora of the Venezuelan Guyana" (J. A. Steyermark, Ed.), p. 45, Botanical Garden Press, Missouri, 1998.
101. F. A. Araújo-Júnior, M. N. Braz, O. G. Rocha-Neto, F. A. Costa, and M. V. H. Brito, *Acta Cir. Bras.* 20, 93 (2005).
102. J. U. Lloyd, "Copaifera Officinalis," The Western Druggist, Chicago, 1898.
103. A. B. Pontes, D. Z. Correia, M. S. Coutinho, and C. G. Mothé, *Rev. Anal.* 7, 36 (2003).
104. B. C. Cavalcanti, L. V. C. Lotufo, M. O. Moraes, R. R. Burbano, E. R. Silveira, K. M. Cunha, V. S. Rao, D. J. Moura, R. M. Rosa, J. A. Henriques, and C. Pessoa, *Food Chem. Toxicol.* 44, 388 (2006).
105. L. V. Montes, L. P. Broseghini, F. S. Andreatta, E. S. Sant'Anna, V. M. Neves, and A. G. Silve, *Nat. On Line* 7, 61 (2009).
106. J. H. Langenheim, "Tropical forest ecosystems in Africa and South America: A Comparative Review" (B. J. Meggers, E. S. Ayensu, and W. D. Duckworth, Eds.), p. 89, Smithsonian Institution Press, Washington, 1973.
107. R. E. Vetter and P. C. Botosso, *IAWA J.* 10, 133 (1989).
108. A. Osol and G. E. Farrar, "The Dispensatory of the United States of America," J.B. Lippincott Co, Philadelphia, 1947.
109. C. Plowden, "The Ecology, Management and Marketing of Non-Timber Forest Products in the Alto Rio Guama Indigenous Reserve (Eastern Brazilian Amazon)," University Park, Penn State University, Ph.D. Degree, 2001.
110. O. C. Rigamonte-Azevedo, P. G. Wadt, and L. H. Wadt, "Copaíba: ecologia e produção de óleo-resina," EMBRAPA, MAPA, Rio Branco, 2004.
111. E. C. P. Oliveira, O. A. Lameira, and M. G. B. Zoghbi, *Rev. Bras. Plantas Med.* 8, 14 (2006).
112. A. C. Leite, "Recomendações para o manejo sustentável do óleo de copaíba," UFAC/SEFE, Rio Branco, 2001.
113. L. A. Ferreira and E. M. Braz, "Avaliação do potencial de extração comercial do óleo-resina de copaíba," The New York Botanical Garden, New York and UFAC, 2001.
114. O. R. Gottlieb, *Rev. Quim. Ind.* 14, 20 (1945).
115. V. Cascon and B. Gilbert, *Phytochemistry* 55, 773 (2000).
116. J. H. Langenheim, "Plant Resins: Chemistry, Evolution, Ecology, and Ethnobotany," Timber Press, Portland, 2003.
117. V. F. Veiga-Júnior, "Controle de Qualidade de Óleos de Copaíba por Cromatografia Gasosa de Alta Resolução," Universidade Federal do Rio de Janeiro, Master degree, 1997.
118. J. A. Duke and J. L. Cellier, "CRC Handbook of Alternative Cash Crops," CRC Press, Boca Raton, 1993.
119. P. Le Cointe, "Arvores e Plantas Uteis," Companhia Editora Nacional, São Paulo, 1947.
120. P. C. Souza Barbosa, L. S. Moreira Wiedemann, R. da Silva Medeiros, P. S. de Tarso Barbosa, G. Vieira, and V. F. Veiga-Júnior, *Chem. Biodivers.* 10, 1350 (2013).
121. J. H. Langenheim, *Am. Sci.* 78, 16 (1990).
122. S. P. Arrhenius and J. H. Langenheim, *Biochem. Syst. Ecol.* 11, 361 (1983).
123. J. H. Langenheim, *Sci.* 163, 1157 (1969).
124. J. J. de Lima Silva, S. B. Guimaraes, E. R. da Silveira, P. R. de Vasconcelos, G. G. Lima, S. M. Torres, and R. C. de Vasconcelos, *Aesthetic. Plast. Surg.* 33, 104 (2009).
125. L. A. Paiva, K. M. A. Cunha, F. A. Santos, N. V. Gramosa, E. R. Silveira, and V. S. N. Rao, *Phytother. Res.* 16, 737 (2002).
126. V. F. Veiga-Júnior, L. Zunino, J. B. Calixto, M. L. Patitucci, and A. C. Pinto, *Phytother. Res.* 15, 476 (2001).
127. R. C. Simonsen, "História Econômica do Brasil: 1500-1820," Metalivros, São Paulo, 1944.
128. E. Carrara-Junior and H. Meirelles, "A Indústria Química e o Desenvolvimento do Brasil: 1500–1889," Metalivros, São Paulo, 1996.
129. V. Salvador, "História do Brasil: 1500–1627," Melhoramentos, São Paulo, 1975.
130. E. Perrot, "Matieres Premieres Usuelles de Règne Vegetal," Masson and Cia, Paris, 1943.
131. E. T. Fonseca, "Óleos vegetais brasileiros," Ministério da Agricultura, Rio de Janeiro, 1927.
132. Food and Drug Administration, "Food Chemical Codex," p. 218, Washington, 1972.
133. A. M. Kligman, *J. Investig. Dermatol.* 47, 393 (1966).
134. M. R. R. Tappin, J. F. G. Pereira, L. A. Lima, A. C. Siani, J. L. Mazzei, and M. F. S. Ramos, *Quim. Nova* 27, 236 (2004).
135. OECD, "OECD Science, Technology and Industry Scoreboard 2013," OECD Publishing, 2013.
136. J. C. Santos, A. C. P. Leite, L. H. O. Wadt, K. H. Borges, F. G. Andrade, and R. S. Menezes, "Demandas Tecnológicas para o Sistema Produtivo do Óleo de Copaíba (Copaífera spp) no Estado do Acre," EMBRAPA, Acre, 2001.
137. B. M. P. Sant'Anna, S. P. Fontes, A. C. Pinto, and C. M. Rezende, *J. Braz. Chem. Soc.* 18, 984 (2007).
138. R. D. Medeiros and G. Vieira, *For. Ecol. Manage* 256, 282 (2008).
139. BRASIL, "Quantidade e valor dos produtos da extração vegetal e da silvicultura, segundo os principais produtos—Brasil–2009," 2011.
140. A. L. Romero, "Contribuição ao conhecimento químico do óleo-Resina de copaíba: configuração absoluta de terpenos," Universidade Estadual de Campinas, Instituto de Química, Campinas, Master Degree, 2007.
141. F. A. Pieri, M. C. Mussi, and M. A. S. Moreira, *Rev. Bras. Plantas Med.* 11, 465 (2009).
142. T. J. Betts, *J. Chromatogr. A* 936, 33 (2001).
143. F. Chen, H. Al-Ahmad, B. Joyce, N. Zhao, T. G. Kollner, J. Degenhardt and C. N. Stewart, Jr., *Plant. Physiol. Biochem.* 47, 1017 (2009).
144. R. Croteau, T. M. Kutchan, and N. G. Lewis, "Natural Products (Secondary Metabolites)," American Society of Plant Physiologists, 2000.
145. E. Pichersky, J. P. Noel, and N. Dudareva, *Science* 311, 808 (2006).
146. F. Bakkali, S. Averbeck, D. Averbeck, and M. Idaomar, *Food Chem. Toxicol.* 46, 446 (2008).
147. V. F. Veiga-Júnior, E. C. Rosas, M. V. Carvalho, M. G. Henriques, and A. C. Pinto, *J. Ethnopharmacol.* 112, 248 (2007).

148. D. O. Dias, M. Colombo, R. G. Kelmann, T. P. Souza, V. L. Bassani, H. F. Teixeira, V. F. Veiga-Júnior, R. P. Limberger, and L. S. Koester, *Anal. Chim. Acta* 721, 79 (2012).

149. V. F. Veiga-Júnior, A. C. Pinto, and M. A. M. Maciel, *Quim. Nova* 28, 3 (2005).

150. A. B. Souza, C. H. Martins, M. G. Souza, N. A. Furtado, V. C. Heleno, J. P. Sousa, E. M. Rocha, J. K. Bastos, W. R. Cunha, R. C. Veneziani, and S. R. Ambrosio, *Phytother. Res.* 25, 215 (2011).

151. J. G. Soares, M. J. C. Vareão, W. Wolter-Filho, A. P. Mourão, A. A. R. Craveiro, and J. C. Alencar, *Acta Amaz.* 9, 65 (2003).

152. A. A. Craveiro, J. G. S. Maia, M. J. C. Varejão, W. W. Filho, A. P. Mourão, and J. W. Alencar, *Acta Amazon.* 8, 705 (1978).

153. M. S. Buckeridge, D. C. Rocha, J. S. G. Reid, and S. M. C. Dietrich, *Physiol. Plant.* 86, 145 (1992).

154. T. T. Franco, N. R. Rodrigues, G. E. Serra, V. R. Panegassi, and M. S. Buckeridge, *J. Chromatogr. B. Biomed. Appl.* 680, 255 (1996).

155. G. Simonetti, "MacDonald Encyclopedia of Herbs and Spices," MacDonald & Co, Verona (1991).

156. M. Fleury, *Acta Bot. Gallica* 144, 473 (1997).

157. M. J. Del Nunzio, *Aerosol Cosmet.* 7, 7 (1985).

158. A. C. Basile, J. A. A. Sertie, P. C. D. Freitas, and A. C. Zanini, *J. Ethnopharmacol.* 22, 101 (1988).

159. J. C. Carvalho, V. Cascon, L. S. Possebon, M. S. S. Morimoto, L. G. V. Cardoso, M. A. C. Kaplan, and B. Gilbert, *Phytother. Res.* 19, 946 (2005).

160. R. M. Fernandes, N. A. Pereira, and L. G. Paulo, *Rev. Bras. Farmacogn.* 73, 53 (1992).

161. F. Gelmini, G. Beretta, C. Anselmi, M. Centini, P. Magni, M. Ruscica, A. Cavalchini, and R. Maffei-Facino, *Int. J. Pharm.* 440, 170 (2013).

162. N. M. B. Brito, M. J. Simões, P. O. Gomes, A. F. Pessoa, and M. C. F. Melo, *Rev. Par. Med.* 13, 12 (1999).

163. L. A. Paiva, V. S. Rao, N. V. Gramosa, and E. R. Silveira, *J. Ethnopharmacol.* 62, 73 (1998).

164. A. F. Bento, R. Marcon, and R. C. Dutra, *Am. J. Pathol.* 178, 1153 (2011).

165. L. A. Paiva, L. A. Gurgel, A. R. Campos, E. R. Silveira, and V. S. Rao, *Life Sci.* 75, 1979 (2004).

166. A. Ohsaki, L. T. Yan, S. Ito, H. Edatsugi, D. Iwata, and Y. Komoda, *Bioorg. Med. Chem. Lett.* 4, 2889 (1994).

167. S. R. Lima, V. F. Junior, H. B. Christo, A. C. Pinto, and P. D. Fernandes, *Phytother. Res.* 17, 1048 (2003).

168. A. C. S. Lourenço, J. E. Baroneza, S. P. Ramos, L. K. Miguel, L. C. Juliani, A. Pic-Taylor, and M. J. S. Salles, *Am. J. Plant. Sci.* 5, 3464 (2014).

169. D. L. Opdyke, *Food Cosmet. Toxicol.* 14, 601 (1976).

170. B. M. Tincusi, I. A. Jiménez, I. L. Bazzocchi, L. M. Moujir, Z. A. Mamani, and J. P. Barroso, *Plant. Med.* 68, 808 (2002).

171. E. N. Alencar, F. H. Xavier-Júnior, A. R. V. Morais, T. R. F. Dantas, N. Dantas-Santos, L. M. Verissimo, V. L. G. Rehder, G. M. Chaves, A. G. Oliveira, and E. S. T. Egito, *J. Nanosci. Nanotechnol.* 15, 880 (2015).

172. A. O. Santos, T. Ueda-Nakamura, B. P. Dias-Filho, V. F. Veiga-Júnior, A. C. Pinto, and C. V. Nakamura, *Mem. Inst. Oswaldo Cruz* 103, 277 (2008).

173. E. C. G. Santos, C. L. Donnici, E. R. Camargos, A. A. Rezende, E. H. Andrade, L. A. Soares, M. Farias L, M. A. R. Carvalho, and M. Almeida, *J. Med. Microbiol.* 62, 1032 (2013).

174. J. Pellegrino, *Exp. Parasitol.* 21, 112 (1967).

175. B. Gilbert, W. B. Mors, P. M. Baker, T. C. B. Tomassini, E. G. Goulart, J. C. Holanda, J. A. R. Costa, J. N. G. Lopes, D. Santos-Filho, S. J. Sarti, A. M. Turco, W. Vichnewski, J. L. C. Lopes, A. W. Thames, J. Pellegrino, and N. Katz, *An. Acad. Bras. Cienc.* 423 (1972).

176. P. Le Cointe, "Árvores e Plantas Úteis: a Amazônia brasileira (III)," Livraria Clássica, Belém, 1934.

177. I. F. B. Martins and A. Silva, *Rev. Pesqui.* 2, 526 (2010).

178. L. R. Estevao, J. P. Medeiros, L. Baratella-Evencio, R. S. Simoes, S. F. Mendonca, and J. Evencio-Neto, *Acta Cir. Bras.* 28, 863 (2013).

179. N. M. Gomes, C. M. Rezende, S. P. Fontes, M. E. Matheus, and P. D. Fernandes, *J. Ethnopharmacol.* 109, 486 (2007).

180. L. A. F. Paiva, L. A. Gurgel, R. M. Silva, A. R. Tome, N. V. Gramosa, and E. R. Silveira, *Vasc. Pharmacol.* 39, 303 (2003).

181. L. A. Paiva, L. A. Gurgel, E. T. Sousa, E. R. Silveira, R. M. Silva, F. A. Santos, and V. S. Rao, *J. Ethnopharmacol.* 93, 51 (2004).

182. E. Y. Yasojima, R. K. Teixeira, P. A. Houat, F. L. Costa, E. L. Silveira, M. V. Brito, and J. G. Lopes-Filho, *Acta Cir. Bras.* 28, 131 (2013).

183. J. Nogueira Neto, M. J. Lindoso, L. F. Coelho, R. A. Carvalho, T. G. Rodrigues, A. G. Araujo, M. J. Girao, and E. Schor, *Acta Cir. Bras.* 26 Suppl 2, 20 (2011).

184. D. L. Medeiros, T. E. V. Lemos, L. H. F. Junior, T. B. S. Montenegro, and P. R. S. Camara, *J. Exp. Integr. Med.* 4, 107 (2014).

185. M. V. Brito, F. D. Costa, D. M. Vasconcelos, L. A. Costa, E. Y. Yasojima, R. K. Teixeira, and V. N. Yamaki, *Acta Cir. Bras.* 29, 776 (2014).

186. R. K. Teixeira, V. N. Yamaki, E. Y. Yasojima, and M. V. Brito, *Acta Cir. Bras.* 28, 526 (2013).

187. N. M. Gomes, C. M. Rezendes, S. P. Fontes, A. M. C. Hovell, R. G. Landgraf, M. E. Matheus, A. C. Pinto, and P. D. Fernandes, *J. Ethnopharmacol.* 119, 179 (2008).

188. C. F. Chicaro, "Análise da expressão da proteína nf-kappaB antes e depois do tratamento com dexametasona e os óleos de copaíba e andiroba em cultura de células de carcinoma epidermóide bucal," Universidade de São Paulo, Departamento de odontologia, São Paulo, Master Degree, 2009.

189. A. D. Garrido, S. P. Cara, M. M. Marques, E. C. Sponchiado-Junior, L. F. Garcia, and M. D. Sousa-Neto, *Dent. Res. J.* 12, 121 (2015).

190. M. V. H. Brito, R. J. Moreira, M. L. C. Tavares, M. C. S. Carballo, T. X. Carneiro, and A. A. S. Santos, *Acta Cir. Bras.* 20, 243 (2005).

191. D. Cabral, Avaliação da atividade antimicrobiana *in-vitro* do óleo-Resina de copaíba (Copaifera duckei Dwyer)," Universidade de Alfenas, Alfenas, Master Degree, 2008.

192. F. A. Pieri, M. C. Mussi, J. E. Fiorini, M. A. Moreira, and J. M. Schneedorf, *Braz. Dent. J.* 23, 36 (2012).

193. A. O. Santos, T. Ueda-Nakamura, B. P. Dias Filho, V. F. Veiga-Júnior, A. C. Pinto, and C. V. Nakamura, *J. Ethnopharmacol.* 120, 204 (2008).

194. A. O. Santos, M. A. Costa, T. Ueda-Nakamura, B. P. Dias-Filho, V. F. Veiga-Júnior, M. M. Souza-Lima, and C. V. Nakamura, *Exp. Parasitol.* 129, 145 (2011).

195. A. O. Santos, T. Ueda-Nakamura, B. P. Dias Filho, V. F. Veiga-Júnior, and C. V. Nakamura, *Evid. Based. Complement. Alternat. Med.* 2012, 898419 (2012).

196. D. C. Soares, N. A. Portella, M. F. Ramos, A. C. Siani, and E. M. Saraiva, *Evid. Based. Complement. Alternat. Med.* 2013, 761323 (2013).

197. J. P. B. Sousa, D. Nanayakkara, A. A. B. Silva, and J. K. Bastos, *J. Pharm. Res.* 5, 4103 (2012).

198. A. P. Brancalion, R. B. Oliveira, J. P. Sousa, M. Groppo, A. A. Berretta, M. E. Barros, M. A. Boim, and J. K. Bastos, *Urol. Res.* 40, 475 (2012).

199. R. B. Oliveira, E. B. Coelho, M. R. Rodrigues, A. R. Costa-Machado, J. P. de Sousa, A. A. Berretta, and J. K. Bastos, *Evid. Based. Complement. Alternat. Med.* 2013, 131372 (2013).

200. F. F. Fernandes and E. de Paula Souza Freitas, *Vet. Parasitol.* 147, 150 (2007).

201. M. D. Baldissera, A. S. Silva, C. B. Oliveira, R. A. Vaucher, R. C. Santos, J. L. Giongo, D. M. Capeleto, A. A. Tonin, and S. G. Monteiro, *Rev. MVZ Cordoba* 19, 4109 (2014).

202. M. D. Baldissera, C. B. Oliveira, A. A. Tonin, P. Wolkmer, S. T. A. Lopes, R. Fighera, M. M. Flores, E. C. P. Oliveira, R. C. V.

Santos, A. A. Boligon, M. L. Athayde, S. G. Monteiro, and A. S. Silva, *Biomed. Prev. Nutr.* 4, 319 (2014).
203. J. R. Mahajan, G. A. L. Ferreira, and J. Pellegrino, *An. Acad. Brasil. Cienc.* 44, 429 (1972).
204. J. R. Mahajan and G. A. L. Ferreira, *An. Acad. Brasil. Cienc.* 43, 611 (1971).
205. J. M. Senedese, J. M. Alves, I. M. Lima, E. A. Andrade, R. A. Furtado, J. K. Bastos, and D. C. Tavares, *BMC Complement. Altern. Med.* 13, 3 (2013).
206. C. G. Sachetti, R. R. Carvalho, F. J. Paumgartten, O. A. Lameira, and E. D. Caldas, *Food Chem. Toxicol.* 49, 1080 (2011).
207. J. A. S. Zuanazzi and P. Mayorga, *Quim. Nova* 33 (2010).
208. V. F. Ferreira, *Quim. Nov.* 23 (2000).
209. J. C. Vié, C. Hilton-Taylor, and S. N. Stuart, "Wildlife in a Changing World—An Analysis of the 2008 IUCN Red List of Threatened Species," IUCN, Switzerland, 2009.
210. R. D. Françoso, R. Brandão, C. C. Nogueira, Y. B. Salmona, R. B. Machado, and G. R. Colli, *Nat. Conserv.* 13, 35 (2015).
211. A. C. C. Valois, *Cad. Cienc. Tecn.* 15, 21 (1998).
212. R. C. Nogueira, H. F. Cerqueira, and M. B. P. Soares, *Expert Opin. Ther. Pat.* 20, 145 (2010).
213. P. Oldham, S. Hall, and O. Forero, *PLoS ONE* 8, e78737 (2013).
214. WHO, "The World Health Report 2013: Research for Universal Health Coverage," World Health Organization, Genebra, 2014.
215. S. H. Kim, N. S. Kim, K. C. Lee, H. B. Lee, and M. S. Kim, *Pak. Vet. J.* 32, 631 (2012).
216. C. A. Joly, C. F. B. Haddad, L. M. Verdade, M. C. Oliveira, V. S. Bolzani, and R. G. S. Berlinck, *Rev. Univ. Sao Paulo* 89, 114 (2011).
217. A. F. P. Ferro, M. B. M. Bonacelli, and A. L. D. Assad, *Gest. Prod.* 13, 489 (2006).
218. R. A. Yunes and J. B. Calixto, "Plantas medicinais - Sob a ótica da química medicinal moderna," Argos, Chapecó, 2001.
219. C. M. O. Simões, E. P. Schenkel, G. Gosmann, J. C. P. Mello, L. A. Mentz, and P. R. Petrovick, "Farmacognosia: da Planta ao Medicamento," UFRGS, Porto Alegre, 1999.
220. C. S. Funari and V. O. Ferro, *Rev. Bras. Farmacogn.* 15, 178 (2005).
221. M. T. Rodrigues, *Cienc. Cult.* 55, 47 (2003).
222. WHO, "Traditional Medicine Strategy: 2014–2023," World Health Organization, Genebra, 2013.
223. BRASIL, "Formulário de Fitoterápicos da Farmacopéia Brasileira / Agência Nacional de Vigilância Sanitária," Anvisa, Brasília, 2011.
224. P. S. Menell, "International Encyclopedia of the Social and Behavioral Sciences" (N. J. S. B. Baltes, Ed.), p. 7615, Pergamon, Oxford, 2001.
225. G. C. Chaves, M. A. Oliveira, L. Hasenclever, and L. M. D. Melo, *Cad. Saude Publica* 23, 257 (2007).
226. K. Lee and S. Lee, *Energ. Policy* 59, 415 (2013).
227. L. L. Mueller and S. M. Taketsuma Costa, *Expert. Opin. Ther. Pat.* 24, 1 (2013).
228. A. R. Santos, C. L. Firme, and J. C. Barros, *Quim. Nova* 31, 445 (2008).
229. P. C. S. Barbosa, R. S. Medeiros, P. T. B. Sampaio, G. Vieira, L. S. M. Wiedemann, and V. F. Veiga-Júnior, *J. Braz. Chem. Soc.* 23, 10 (2012).
230. G. Filoche and F. Pinton, *J. Agrar. Change* 14, 380 (2014).
231. L. F. Alves, *Rev. Virtual Quim.* 5, 450 (2013).
232. H. Ernst, *World Patent Information* 25, 233 (2003).
233. G. A. Cordell, *Phytochem. Lett.* 10, 28 (2014).
234. J. Hudson and H. F. Khazragui, *Drug Discov. Today* 18, 610 (2013).
235. C. Kobayashi, T. O. Fontanive, B. G. Enzweiler, L. R. Bona, T. Massoni, M. A. Apel, A. T. Henriques, M. F. Richter, P. Ardenghi, and E. S. Suyenaga, *Pharm. Biol.* 49, 306 (2011).
236. C. H. Jáuregui, M. A. Casado, M. G. B. Zoghbi, and R. C. M. Silva, *Chem. Biodivers.* 8, 674 (2011).
237. J. P. Sousa, A. P. Brancalion, A. B. Souza, I. C. Turatti, S. R. Ambrósio, N. A. Furtado, N. P. Lopes, and J. K. Bastos, *J. Pharm. Biomed. Anal.* 25, 653 (2011).
238. E. E. Balbinol and M. F. Dias, *Rev. Bras. Farmacogn.* 20, 992 (2010).
239. RENISUS, "Relação Nacional de Plantas Medicinais de Interesse ao SUS. Espécies vegetais," Ministério da Saúde, Brazil, 2013.
240. Z. Siegfried, Complete Equipment for Urethritis (Inflammation of the Urethra, Gonorrhoea), GB189803261, 1898.
241. A. Courmontagne and P. S. Francois, Nouvelles Compositions Cosmetíques ou Alimentaires Renfermant du Copaiba, FR2692480, 1993.
242. P. S. Francois and A. Courmontagne, Cosmetic or Food Compositions Containing Copaiba, WO9400105, 1994.
243. S. R. Fogg and T. R. Kapsner, Method of Coloring Hair or Eyelashes with Compositions Which Contain Metal Containing Pigments and a Copaiba Resin, US5888251, 1999.
244. A. Shunichi, H. Masakatsu, O. Kouichi, A. Katsutoshi, and K. Shigeto, Deodorant, JP2002255774, 2002.
245. U. Chiyoko and H. Tatsuo, Agent for Preventing and Improving Gray Hair, JP2000169348, 2000.
246. Y. Eiichiro, K. Hisayuki, S. Yuki, N. Masako, and F. Minoru, Skin External Preparation, JP8012560, 1996.
247. S. R. Fogg, T. R. Kapsner, and P. Matravers, Methods of Coloring Hair or Eyelashes with Compositions Which Contain Metal Containing Pigments and a Copaiba Resin, US6045589, 2000.
248. H. Hiroshi, H. Tomonori, N. Maki, and T. Satoshi, Skin Care Preparation, JP2001322941, 2001.
249. M. Kubota, R. Komaki, Y. Yamashita, O. Ito, and Y. Ichikawa, Perfume Composition, JP2006002059, 2006.
250. B. J. Kenupp, B. A. R. Fi, B. J. Claudino, B. L. P. Flores, and C. J. C. Tavares, Process to Obtain Extracts, Fractions and Isolated Compounds from Copaifer Species and Their Use for the Treatment of Urinary Lithiasis in Human Beings and Animals, WO2005110446, 2005.
251. A. D. Garrido, R. C. Lia, S. C. Franca, J. F. Silva, S. Astolfi-Filho, and M. D. Sousa-Neto, *Int. Endod. J.* 43, 283 (2010).
252. C. A. C. G. Simões, Método de fabricação de um gel de óleo de copaíba (Copaifera multijuga) com atividade antibacteriana para controle de placa ou biofilme dental, BR04042662, 2006.
253. D. Q. Gerolano and J. Q. Gimenes, Pomada de copaíba, BR8605738, 1988.
254. C. A. Harger, Tratamento de hemorróidas, com óleo vegetal extraído de plantas da espécie das copaíferas (copaíba), MU82032343, 2002.
255. B. M. Sparling, Medicinal Preparation, GB637440, 1950.
256. N. Yuninaga, T. Norihiro, K. Shinko, W. Kanae, and A. Hiroshi, External Preparation for Skin and Bathing Agent, JP07278001, 1995.
257. J. C. T. Carvalho, Composição farmacêutica a base de óleo de copaíba padronizado (copaifera ssp) para tratamento de afecções ginecológicas, PI10042768, 2010.
258. FIOCRUZ, "A saúde no Brasil em 2030: Diretrizes para a prospecção estratégica do sistema de saúde brasileiro." Fiocruz, Ipea, Ministério da Saúde, Secretaria de Assuntos Estratégicos da Presidência da República, Rio de Janeiro, 2012.
259. A. A. Date, N. Desai, R. Dixit, and M. Nagarsenker, *Nanomed.* 5, 1595 (2010).
260. B. Singh, S. Bandopadhyay, R. Kapil, R. Singh, and O. Katare, *Crit. Rev. Ther. Drug Carrier Syst.* 26, 427 (2009).
261. J. Wadhwa, A. Nair, and R. Kumria, *Acta Pol. Pharm.* 69, 179 (2012).
262. M. A. M. Maciel, M. L. Medeiros, I. Araujo-Filho, C. G. F. T. Rossi, C. C. M. Salgueiro, and V. F. Veiga-Júnior, Nanoformulação contendo bioativos naturais para cicatrização de lesões cutâneas, BR1020140331336, 2014.
263. M. L. Medeiros, M. A. M. Maciel, I. Araujo-Filho, A. C. M. Rego, D. P. Emerenciano, and V. F. Veiga-Júnior, Preparo e avaliação de bioformulação contendo óleo de copaíba para tratamento de enfermidades cutâneas, BR1020140331328, 2014.

264. M. L. Medeiros, M. A. M. Maciel, R. A. Carvalho, I. A. Filho, A. C. M. Rêgo, M. M. Marques, C. D. Soares, and V. F. Veiga-Júnior, Óleo de copaíba bioformulado em sistema SMEDDS para aplicação odontológica, BR1020150132310, 2015.

265. A. R. F. Brunharoto, J. K. Bastos, and A. A. B. E. Silva, Processo de obtenção de micropartículas matriciais de copaífera langsdorffii (partes aéreas) e isolamento dos princípios ativos; micropartículas e compostos assim obtidos, com atividade antilitiásica (cálculo renal), analgésica, anti-espasmódica, anti-inflamatória, diurética e anti-séptica, suas formulações, produtos e usos, WO2011120118, 2011.

266. F. H. Xavier-Júnior, K. G. H. Silva, I. E. G. Farias, A. R. V. Morais, E. N. Alencar, I. B. Araújo, A. G. Oliveira, and E. S. T. Egito, *J. Drug Del. Sci. Tech.* 22, 367 (2012).

267. L. G. Lucca, S. P. Matos, B. T. Borille, D. D. O., H. F. Teixeira, V. F. Veiga-Júnior, R. P. Limberger, and L. S. Koester, *J. Pharm. Biomed. Anal.* 104, 144 (2015).

268. D. O. Dias, M. Colombo, R. G. Kelmann, S. Kaiser, L. G. Lucca, H. F. Teixeira, R. P. Limberger, V. F. Veiga-Júnior, and L. S. Koester, *Ind. Crops. Prod.* 59, 154 (2014).

269. C. L. Morelli, M. Mahrous, M. N. Belgacem, M. C. Branciforti, and R. E. S. Bretas, *J. Bras. Ind. Crops. Prod.* 70, 134 (2015).

270. E. C. R. Rodrigues, A. M. Ferreira, J. C. E. Vilhena, F. B. Almeida, R. A. S. Cruz, A. C. Florentino, R. N. P. Souto, J. C. T. Carvalho, and C. P. Fernandes, *Rev. Bras. Farmacogn.* 24, 699 (2014).

271. T. Stupp, R. A. Freitas, M. R. Sierakowski, F. C. Deschamps, A. Wisniewski-Jr, and M. W. Biavatti, *Bioresour. Technol.* 99, 2659 (2008).

272. E. Y. Yasojima, R. K. Teixeira, P. A. Houat, F. L. Costa, V. N. Yamaki, D. J. Feitosa-Junior, C. A. Silva, and M. V. Brito, *Arq. Bras. Cir. Dig.* 28, 186 (2015).

273. P. F. Silva, M. V. Brito, F. S. Pontes, S. R. Ramos, L. C. Mendes, and L. C. Oliveira, *Acta Cir. Bras.* 30, 120 (2015).

274. L. N. Lopes, F. A. Santos, L. C. Oliveira, S. Percario, C. A. Barros, and M. V. Brito, *Acta Cir. Bras.* 30, 568 (2015).

275. K. B. Santiago, B. J. Conti, B. F. M. T. Andrade, J. J. M. Silva, H. L. Rogez, E. J. Crevelin, L. A. B. Moraes, R. Veneziani, S. R. Ambrosio, J. K. Bastos, and J. M. Sforcin, *Biomed. Pharmacother.* 70, 12 (2015).

276. A. Volpato, R. K. Grosskopf, R. C. Santos, R. A. Vaucher, R. P. Raffin, A. A. Boligon, M. L. Athayde, L. M. Stefani, and A. S. Silva, *J. Essent. Oil Res.* 27, 244 (2015).

277. P. L. Tobouti, M. C. Mussi, D. C. Rossi, F. M. Pigatti, C. P. Taborda, L. A. A. Taveira, and S. C. Sousa, *Gerodontology* 31, 1 (2014).

278. F. L. Westphal, M. Canzian, F. A. Pieri, A. C. Reichl, P. M. Pego-Fernandes, L. C. Lima, and V. F. Veiga-Júnior, *Biomed. Res. Int.* 2014, 939738 (2014).

279. E. S. Gonçalves, J. R. Silva, C. L. Gomes, M. B. L. Nery, D. M. A. F. Navarro, G. K. N. Santos, J. C. Silva-Neto, J. H. Costa-Silva, A. V. Araújo, and A. G. Wanderley, *Rev. Bras. Farmacogn.* 24, 355 (2014).

280. R. Amilia Destryana, D. Gary Young, C. Woolley, T.-C. Huang, H.-Y. Wu, and W.-L. Shih, *J. Am. Oil Chem. Soc.* 91, 1531 (2014).

281. N. M. Botelho, E. L. Silveira, L. N. Lopes, F. A. Santos, R. K. Teixeira, and T. T. Silva, *Acta Cir. Bras.* 29, 528 (2014).

282. D. L. Medeiros, T. E. V. Lemos, F. K. S. Araujo, T. B. S. Montenegro, L. H. F. Junior, and P. R. S. Camara, *J. Exp. Integr. Med.* 4, 194 (2014).

283. D. S. Dias, L. B. Fontes, A. E. Crotti, B. J. Aarestrup, F. M. Aarestrup, A. A. Silva-Filho, and J. O. Correa, *Molecules* 19, 12814 (2014).

284. D. C. Zimmermam-Franco, E. B. Bolutari, H. C. Polonini, A. M. Carmo, M. Chaves, and N. R. Raposo, *Molecules* 18, 12561 (2013).

285. C. M. A. Vilanova, S. M. Ribeiro, R. C. S. Machado, S. M. Vieira, S. G. Lima, P. H. M. Nunes, and M. C. C. Martins, *Emir. J. Food Agric.* 25, 394 (2013).

286. N. M. Botelho, S. C. Correa, R. C. Lobato, R. K. Teixeira, and J. A. Quaresma, *Acta Cir. Bras.* 28, 185 (2013).

287. E. Izumi, T. Ueda-Nakamura, V. F. Veiga-Júnior, and C. V. Nakamura, *Planta Med.* 79, 952 (2013).

288. D. C. Soares, N. A. Portella, M. F. Ramos, A. C. Siani, and E. M. Saraiva, *Evid. Based. Complement. Alternat. Med.* 2013, 761323 (2013).

289. M. A. D. Silva, A. C. Pereira, M. C. Marin, and M. A. Salgado, *J. Clin. Exp. Dent.* 5, 169 (2013).

290. D. S. Masson, S. L. Salvador, A. C. M. Polizello, and M. A. C. Frade, *Rev. Bras. Plantas Med.* 15, 664 (2013).

291. P. C. S. Barbosa, L. S. M. Wiedemann, R. S. Medeiros, P. T. B. Sampaio, G. Vieira, and V. F. Veiga-Júnior, *Chem. Biodivers.* 10, 1350 (2013).

292. A. A. V. O. Sousa, F. D. Lima, A. A. Machado, M. O. Vera, L. M. P. Fernandes, R. R. Lima, and C. S. F. Maia, *J. Neurol. Sci.* 333 (2013).

293. M. R. Almeida, J. D. Darin, L. C. Hernandes, M. F. S. Ramos, L. M. Antunes, and O. Freitas, *Genet. Mol. Biol.* 35, 664 (2012).

294. A. Guimarães-Santos, D. S. Santos, I. R. Santos, R. R. Lima, A. Pereira, L. S. Moura, R. N. Carvalho-Jr, O. Lameira, and W. G. Leal, *Evid. Based. Complement. Alternat. Med.* 2012, 918174 (2012).

295. J. S. Prophiro, M. A. Silva, L. A. Kanis, L. C. Rocha, J. E. Duque-Luna, and O. S. Silva, *Parasitol. Res.* 110, 699 (2012).

296. J. S. Prophiro, M. A. Silva, L. A. Kanis, B. M. Silva, J. E. Duque-Luna, and O. S. Silva, *Parasitol. Res.* 110, 713 (2012).

297. J. Nogueira-Neto, M. J. Lindoso, L. F. Coelho, R. A. Carvalho, T. G. Rodrigues, A. G. Araujo, M. J. Girao, and E. Schor, *Acta Cir. Bras.* 26, 20 (2011).

298. E. Comelli-Junior, J. Skinovski, M. F. Sigwalt, A. B. Branco, S. R. Luz, and P. Baule Cde, *Acta Cir. Bras.* 25, 362 (2010).

299. N. M. Brito, M. V. Brito, K. Carvalho Rde, L. T. Matos, R. C. Lobato, S. C. Correa, and R. B. Brito, *Acta Cir. Bras.* 25, 176 (2010).

300. R. J. A. Deus, A. S. C. Carvalho, D. A. D. S. Banna, M. S. P. Arruda, C. N. Alves, and A. S. Santos, *Rev. Bras. Pl. Med.* 11, 347 (2009).

301. M. Curio, H. Jacone, J. Perrut, A. C. Pinto, V. F. Filho, and R. C. Silva, *J. Pharm. Pharmacol.* 61, 1105 (2009).

302. R. C. Vieira, E. Bombardiere, J. J. Oliveira, R. S. Lino-Júnior, L. A. B. Brito, and A. P. Junqueira-Kipnis, *Vet. Immunol. Immunopathol.* 128, 319 (2009).

303. R. C. Vieira, E. Bombardiere, J. J. Oliveira, R. S. Lino-Júnior, L. A. B. Brito, and A. P. Junqueira-Kipnis, *Pesqui. Vet. Bras.* 28, 358 (2008).

304. M. W. Biavatti, D. Dossin, F. C. Deschamps, and M. P. Lima, *Rev. Bras. Farmacogn.* 16, 230 (2006).

305. E. S. O. Castro, S. Zucoloto, F. S. Ramalho, L. N. Ramalho, J. M. Reis, A. A. Bastos, and M. V. Brito, *Phytother. Res.* 18, 92 (2004).

306. N. M. B. Brito, L. Kulay-Júnior, M. J. Simões, O. A. Lameira, L. G. Lamarão, and S. H. B. Damous, *Rev. Bras. Ginecol. Obstet.* 22, 489 (2000).

307. V. Cascon and B. Gilbert, *Phytochemistry* 55, 773 (2000).

308. N. M. B. Brito, M. J. Simões, A. F. Pessoa, and M. C. F. Melo, *Rev. Para. Med.* 12, 28 (1998).

309. A. G. Batista, A. S. Ferrari, D. C. Cunha, J. K. Silva, C. B. Cazarin, L. C. Correa, M. A. Prado, L. B. Carvalho-Silva, E. A. Esteves, and M. R. Marostica-Junior, *Food Chem.* 197, 1153 (2016).

310. M. Lemos, J. R. Santin, C. S. Mizuno, T. Boeing, J. P. B. Sousa, D. Nanayakkara, J. K. Bastos, and S. F. Andrade, *Rev. Bras. Farmacogn.* 25, 238 (2015).

311. B. Adzu, S. O. Balogun, E. Pavan, S. D. Ascencio, I. M. Soares, R. W. Aguiar, R. V. Ribeiro, A. M. Beserra, R. G. Oliveira, L. I. Silva, A. S. Damazo, and D. T. Martins, *J. Ethnopharmacol.* 175, 378 (2015).

312. J. R. S. Botelho, A. G. Santos, M. E. Araújo, M. E. M. Braga, W. Gomes-Leal, R. N. Carvalho Junior, M. A. A. Meireles, and M. S. Oliveira, *J. Supercrit. Fluids* 98, 167 (2015).

313. M. S. Nogueira, R. A. Furtado, and J. K. Bastos, *J. Agric. Food. Chem.* 63, 6939 (2015).

314. R. A. Furtado, C. T. Bernardes, M. N. Silva, K. F. Zoccal, L. H. Faccioli, and J. K. Bastos, *Biomed. Res. Int.* 2015, 913152 (2015).

315. J. M. Alves, C. C. Munari, B. M. N. M. Azevedo, R. A. Furtado, J. M. Senedese, J. K. Bastos, and D. C. Tavares, *J. Appl. Toxicol.* 33, 854 (2013).

316. A. R. M. Costa-Machado, J. K. Bastos, and L. A. P. Freitas, *Rev. Bras. Farmacogn.* 23, 79 (2013).

317. A. P. Brancalion, R. B. Oliveira, J. P. Sousa, M. Groppo, A. A. Berretta, M. E. Barros, M. A. Boim, and J. K. Bastos, *Urol. Res.* 40, 475 (2012).

318. F. T. T. Trindade, R. G. Stabeli, A. A. Pereira, V. A. Facundo, and A. A. Silva, *Rev. Bras. Farmacogn.* 23, 464 (2013).

319. F. S. Vargas, P. D. O. Almeida, E. S. Aranha, A. P. A. Boleti, P. Newton, M. C. Vasconcellos, V. F. Veiga-Júnior, and E. S. Lima, *Molecules* 20, 6194 (2015).

320. M. G. Sarpietro, A. Di Sotto, M. L. Accolla, and F. Castelli, *Thermochim. Acta* 600, 28 (2015).

321. M. I. Campos, W. D. Vieira, C. N. Campos, F. M. Aarestrup, and B. J. Aarestrup, *Mol. Clin. Oncol.* 3, 825 (2015).

322. R. Lama, B. Zhong, D. G. Kulman, and B. Su, *Phytochem. Lett.* 10, 65 (2014).

323. A. B. Souza, M. G. Souza, M. A. Moreira, M. R. Moreira, N. A. Furtado, C. H. Martins, J. K. Bastos, R. A. Santos, V. C. Heleno, S. R. Ambrosio, and R. C. Veneziani, *Molecules* 16, 9611 (2011).

324. R. Geris, I. G. Silva, H. H. Silva, A. Barison, E. Rodrigues-Filho, and A. G. Ferreira, *Rev. Inst. Med. Trop. Sao Paulo* 50, 25 (2008).

325. V. F. Veiga-Júnior, L. Zunino, M. L. Patitucci, A. C. Pinto, and J. B. Calixto, *J. Pharm. Pharmacol.* 58, 1405 (2006).

326. K. M. A. Cunha, L. A. Paiva, F. A. Santos, N. V. Gramosa, E. R. Silveira, and V. S. Rao, *Phytother. Res.* 17, 320 (2003).

327. B. M. Tincusi, I. A. Jimenez, I. L. Bazzocchi, L. M. Moujir, Z. A. Mamani, J. P. Barroso, A. G. Ravelo, and B. V. Hernandez, *Planta Med.* 68, 808 (2002).

328. L. A. Paiva, L. A. Gurgel, R. M. Silva, A. R. Tome, N. V. Gramosa, E. R. Silveira, F. A. Santos, and V. S. Rao, *Vascul. Pharmacol.* 39, 303 (2002).

329. G. Svetlichny, I. C. Kulkamp-Guerreiro, S. L. Cunha, F. E. Silva, K. Bueno, A. R. Pohlmann, A. M. Fuentefria, and S. S. Guterres, *Pharmazie* 70, 155 (2015).

330. P. K. Gupta, A. K. Jaiswal, S. Asthana, B. V. Teja, P. Shukla, M. Shukla, N. Sagar, A. Dube, S. K. Rath, and P. R. Mishra, *Br. J. Pharmacol.* 172, 3596 (2015).

331. R. F. Bonan, P. R. Bonan, A. U. Batista, F. C. Sampaio, A. J. Albuquerque, M. C. Moraes, L. H. Mattoso, G. M. Glenn, E. S. Medeiros, and J. E. Oliveira, *Mater. Sci. Eng. C. Mater. Biol. Appl.* 48, 372 (2015).

332. C. G. Venturini, F. A. Bruinsmann, R. V. Contri, F. N. Fonseca, L. A. Frank, C. M. D'Amore, R. P. Raffin, A. Buffon, A. R. Pohlmann, and S. S. Guterres, *Eur. J. Pharm. Sci.* 79, 36 (2015).

333. R. A. Vaucher, J. L. Giongo, L. P. Bolzan, M. S. Côrrea, V. P. Fausto, C. F. S. Alves, L. Q. S. Lopes, A. A. Boligon, M. L. Athayde, A. P. Moreira, A. Brandelli, R. P. Raffin, and R. C. V. Santos, *J. Asia Pac. Entomol.* 18, 205 (2015).

334. J. H. Silva, V. R. Borges, C. L. Pereira, R. Ferrari, R. M. Mattos, E. G. Barros, C. Y. Palmero, P. D. Fernandes, P. R. Carvalho, V. P. Sousa, L. M. Cabral, and L. E. Nasciutti, *J. Pharm. Pharmacol.* 67, 1744 (2015).

335. F. G. G. Dias, L. A. Casemiro, C. H. G. Martins, L. G. G. G. Dias, L. F. Pereira, L. T. Nishimura, F. F. Souza, and C. S. Honsho, *Cienc. Rural* 45, 1073 (2015).

336. H. O. Carvalho, C. S. Lima, A. A. Sanches, J. O. D. Silva, C. P. Fernandes, and J. C. T. Carvalho, *J. App. Pharm. Sci.* 5, 001 (2015).

337. D. O. Dias, M. Colombo, R. G. Kelmann, S. Kaiser, L. G. Lucca, H. F. Teixeira, R. P. Limberger, V. F. Veiga-Júnior, and L. S. Koester, *Ind. Crop. Prod.* 59, 154 (2014).

338. D. Masson-Meyers, C. S. Enwemeka, V. Bumah, T. Andrade, and M. A. Frade, *International Journal of Phytomedicine* 5, 378 (2013).

339. A. L. G. Millas, R. McKean, R. Stevens, M. Yusuf, J. V. W. Silveira, M. B. Puzzi, and E. Bittencourt, *J. Biomater. Tissue Eng.* 4, 217 (2013).

340. D. S. Masson-Meyers, T. A. M. Andrade, S. N. Leite, and M. A. C. Frade, *Inter. J. Nat. Prod. Sci.* 3, 10 (2013).

341. D. S. Masson-Meyers, C. S. Enwemeka, V. V. Bumah, T. A. M. Andrade, S. E. Cashin, and M. A. C. Frade, *Int. J. Appl. Microbiol. Sci.* 2, 9 (2013).

342. F. H. Xavier-Júnior, K. G. H. Silva, I. E. G. Farias, A. R. V. Morais, E. N. Alencar, I. B. Araujo, A. G. Oliveira, and E. S. T. Egito, *J. Drug Deliv. Sci. Technol.* 22, 367 (2012).

343. A. G. Silva, F. P. Puziol, R. N. Leitao, T. R. Gomes, R. Scherer, M. L. Martins, A. S. Cavalcanti, and L. C. Cavalcanti, *Altern. Med. Rev.* 17, 69 (2012).

344. L. Garcia, S. Cristiane, M. Wilson, M. Soraya, R. A. Lopes, R. Monica, and O. Freitas, *J. Conserv. Dent.* 14, 108 (2011).

345. C. S. Lima, B. J. Medeiros, H. A. Favacho, K. C. Santos, B. R. Oliveira, J. C. Taglialegna, E. V. Costa, K. J. Campos, and J. C. Carvalho, *Phytomedicine* 18, 1013 (2011).

346. S. L. Pereira, C. S. Barros, T. D. Salgado, V. P. Filho, and F. N. Costa, *J. Contemp. Dent. Pract.* 11, E057 (2010).

347. L. R. M. Estevão, J. P. Medeiros, M. V. R. Scognamillo-Szabó, L. Baratella-Evêncio, E. C. Guimarães, C. A. G. Câmara, and J. Evêncio-Neto, *Pesq. Agropec. Bras.* 44, 406 (2009).