Chapter 4

Biological Properties of Essential Oils from the *Piper* Species of Brazil: A Review

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Abstract

Piperaceae, a Latin name derived from Greek, which in turn originates from the Arabic word *babary*—black pepper, is considered one of the largest families of basal dicots, found in tropical and subtropical regions of both hemispheres. The species that belong to this family have a primarily pantropical distribution, predominantly herbaceous members, occurring in tropical Africa, tropical Asia, Central America and the Amazon region. The Piperaceae family includes five genera: *Piper*, *Peperomia*, *Manekia*, *Zippelia* and *Verhuellia*. Brazil has about 500 species distributed in the *Piper*, *Peperomia* and *Manekia* genera. The *Piper* genus, the largest of the Piperaceae family, has about 4000 species. Within the *Piper* genus, about 260–450 species can be found in Brazil. *Piper* species have diverse biological activities and are used in pharmacopeia throughout the world. They are also used in folk medicine for treatment of many diseases in several countries including Brazil, China, India, Jamaica and Mexico. Pharmacological studies of *Piper* species point toward the vast potential of these plants to treat various diseases. Many of these species are biologically active and have shown antitumor, antimicrobial, antioxidant, insecticidal, anti-inflammatory, antinociceptive, enzyme inhibitor, antiparasitic, antiplatelet, piscicide, allelopathic, antiophidic, anxiolytic, antidepressant, antidiabetic, hepatoprotective, amebicide and diuretic possibilities.

Keywords: Piperaceae, *Piper*, essential oils, biological activities, chemical constituents

1. Introduction

Nature, in general, has produced most of the known organic substances. Among the various kingdoms of nature, the plant kingdom has contributed most significantly to the supply of secondary metabolites. For example, essential oils derived from plants have great value due to their applications as medicines, cosmetics, food and agrochemicals [1, 2].

Essential oils constitute a complex mixture of low molecular weight substances (usually less than 500 Da) obtained by hydrodistillation or by extraction with organic solvents [2, 3]. A single plant may contain between 20 and 100 secondary metabolites belonging to different chemical classes. Terpenoids, phenylpropanoids and aromatic compounds are metabolites present in essential oils [2]. Among the terpenoids, monoterpenes and sesquiterpenes make up the largest group of substances in essential oils [2, 4].

About 3000 essential oils are produced using less than 2000 plant species, among which 300 are important from a commercial point of view. Essential oil production is 40,000–60,000 tons/year with a market value estimated at $700 million, indicating an increase in production and essential oil consumption worldwide [2].

In Brazil, the production of essential oils began at the end of the second decade of the twentieth century based on the extraction of native species to meet the demands of the foreign market. Interest in essential oils is based not only on the possibility of obtaining aromatic compounds (pleasant odor) and the application of products such as perfumes, fragrances and cosmetics, but also on possessing therapeutic properties such as insecticides, fungicides, bactericides or a precursor compound of molecules with high added value [5].

2. Piperaceae family

Piperaceae is a Latin name derived from Greek, which in turn originates from the Arabic babary, which means black pepper. It is considered one of the largest families of basal dicots, present in tropical and subtropical regions of both hemispheres [5]. In this family, there are species with a primarily pantropical distribution, having mostly herbaceous representatives (vines, shrubs and even some trees) [5, 6].

This family includes five genera: *Piper*, *Peperomia*, *Manekia*, *Zippelia* and *Verhuellia* [7]. They are present in tropical Africa, tropical Asia, Central America and the Amazon region [6]. Brazil is represented by about 500 species distributed in the *Piper*, *Peperomia* and *Manekia* genera [8]. The family is very important as a source of substances with pharmacological activities [9]. Many chemical compounds such as amides, phenylpropanoids, chromone, lignans and neolignans have been found [10].

3. *Piper* genus

Piper is the largest genus of the Piperaceae family [7, 11]. The species of this genus have diverse biological activities and are used in pharmacopeia throughout the world. They are also used in folk medicine for treatment of many diseases in several countries including Brazil, China, India, Jamaica and Mexico [9–11].

In Brazil, *Piper* species are distributed throughout the national territory. Among the aromatic flora of the Amazon region, there are more than a dozen species that provide essential oils that are used by the population for therapeutic purposes [12]. The decoction of *Piper callosum* leaves is used to treat diseases of the gastrointestinal tract [5, 13, 14]. Moreover, the tea of the decoction of *Piper hispidum* leaves is useful for the treatment of malaria. *Piper marginatum* is used as a tonic, carminative, stimulant, diuretic and sudorific agent against stomach, liver and gallbladder pain, toothaches, and snake and insect bites [5, 15, 16]. *Piper cavalcantei* Yuncker is called "electric sky" or "electric oil". The decoction of its leaves is considered an excellent antipyretic and analgesic, especially for headaches. The infusion of the leaves is used as an antidiarrheal, to prevent dehydration and to combat menstrual cramps. Oil, extracted by soaking and heating, is used topically for earaches and other external pain [17].

The *Piper* species found in the Northeast of Brazil also have many uses in folk medicine, such as *Piper corcovadensis* used for toothaches [11]. The species found in the Atlantic rainforest are also used. For example, *Piper regnellii* (L.) Miq. is used as an anesthetic and anti-inflammatory agent. *Piper cernuum* Vell. is used as an analgesic (mainly for stomach aches) against liver and kidney diseases. Chewing the leaves of *Piper gaudichaudianum* Kunth. fights toothaches, while *Piper cf. lhostzkyanum* Kunth. is used to combat pain in the stomach, liver and kidney [17].

The decoction of *Piper umbellatum* leaves is used by those in the working class especially in the treatment of diseases in the digestive, urinary and respiratory tracts, and treatment of stomatitis, vaginitis and liver disorder [18, 19]. *Piper aduncum*, popularly known as pimenta-de-macaco and aperta-ruão, has been used in the treatment of gynecological diseases and intestinal disorders [14]. *Piper* sp, known as Jaborandi, is used to treat toothaches [19]. *Peperomia pellucida* H.B.K., popularly known as folha-de-vidro, is used against gastrointestinal ailments and high blood pressure and acts as a mild diuretic. The juice of the plant can be used to treat ocular diseases in general [20].

Many *Piper* species are biologically active and have shown antitumor [21], antimicrobial [22], antioxidant, insecticide, larvicide [5], anti-inflammatory, antinociceptive, enzyme inhibitor, trypanocidal, antiplatelet, piscicide, allelopathic, antiophidic, anti-malaria, antileishmania, ansiliotico/antidepressant, antituberculosis, antidiabetic, nematocide, herbicide, hepatoprotective, anti-*Helicobacter pylori* [23], amebicide [24] and diuretic [25] potential.

Piperaceae's contribution to scientific and technological knowledge is considered very significant. Chemistry studies of *Piper* species have led to the identification of a variety of new chemical compounds belonging to different classes, including alkaloids [26], amides [27], chromenes [28], derivatives of benzoic acids [29], lignans, neolignans, propenyl phenols, terpenes, steroids, chalcones, diidrochalcones, flavones, flavanones, kavalactones, piperolides, ceramides, fatty acids [5, 10] and flavonoids [23, 26].

4. Chemical composition of essential oils of the *Piper* species from Brazil

From a chemical point of view, essential oils are complex mixtures of volatile substances that are lipophilic and usually odoriferous and liquid. They are endowed with aromas that are almost always pleasant and colorless when recently extracted [29]. They can contain from 20 to 60 or more different compounds at various concentrations [30].

The composition of essential oils is constantly being transformed, according to seasonal variation and circadian rhythms. It may also be determined by genotype, environmental factors, and plant cultivation and collection procedures. It can vary according to geographical origin, drying, harvest time, type of fertilizer, but the main components responsible for the aroma seem to remain constant [31].

The *Piper* essential oils are characterized by the presence of monoterpenes, sesquiterpenes and phenylpropanoids with significant biological effects [10]. Essential oils of many *Piper* species in Brazil have been studied for their chemical composition (**Table 1**). We highlight the following species:

An analysis of the essential oil from the leaves and stem of a *P. marginatum* specimen collected in the city of Itacoatiara in the state of Amazonas showed the presence of the following: safrole (0.51 and 0.10%); 3,4-(methylenedioxy) propiophenone (8.01 and 8.92%); 2-methoxy-4,5-(methylenedioxy) propiophenone (1.10 and 1.35%); β-caryophyllene (4.01 and 5.57%); elemicin (1.32 and 1.53%); α-terpinene (0.73 and 0.45%); (*E*)-ocimene (2.31 and 0.68%); α-terpinolene (1.11 and 0.85%); myristicin (0.23 and 9.23%); α-pinene (0.84 and 0.68%); α-copaene (2.47 and 1.71%); γ-elemene (3.75% and trace) and α-humulene (1.34 and 0.59%) [47].

In Ref. [34], 35 constituents were identified in the essential oil from the leaves and stem of *Piper aleyreanum* collected in Porto Velho in the state of Rondônia and reported as the major components: caryophyllene oxide (11.5%), β-pinene (9%), spathulenol (6.7%), camphene (5.2%), β-elemene (4.7%), myrtenal (4.2%), verbenone (3.3%) and pinocarvone (3.1%).

In Ref. [48] mainly non-oxygenated sesquiterpenes were identified in the chemical composition of the essential oil of seven *Piper* species of the Brazilian Atlantic Forest, with *E*-caryophyllene and germacrene D being the most frequent. However, the non-oxygenated monoterpenes (*Z*)-β-ocimene, α-pinene and β-pinene were also present.

From the literature about the phytochemical study of the essential oil of *Piper tuberculatum* extracted from the fruit and fine stems from a specimen collected in Rondônia, the predominance of sesquiterpenes was demonstrated, with caryophyllene oxide (32.1 and 26.6%) and (*E*)-caryophyllene (17.7 and 12.3%) as the major compounds [48].

According to Ref. [49], the essential oil from the leaves of *P. aduncum* collected in the city of Bocaiuva, in the state of Minas Gerais, has as major constituents the compounds 1,8-cineole (55.8%), α-terpineol (5.9%), (*E*)-ocimene (4.8%), (*E*)-pinene (4.7%) and α-pinene (4.5%). The composition analysis of the essential oil from the leaves of *Piper hispidinervum* and *P. callosum* collected in the Amazon showed that both species have safrole (98.12 and 64%) as the major constituent [12].

The study of the essential oil of three *Piper* species collected in different areas of the Federal District revealed the predominance of sesquiterpenes in all species. In the essential oil of *Piper arboreum*, the only monoterpenes identified were δ-3-carene (0.9%) and linalool (1.1%). The constituents present in the highest concentrations were bicyclogermacrene (12.1%), 10-epi-γ-eudesmol (11.6%), spathulenol (8.4%), caryophyllene oxide (10.1%)

Species	Part of plant used	Main chemical compounds	Biological properties	References
Piper angustifolium	Leaves	Spathulenol; caryophyllene oxide	Anti-leishmania (*Leishmania infantum*)	[32]
P. anonifolium	Aerial parts	α-pinene; β-selinene; α-selinene; selin-11-en-4-α-ol	Cytotoxic; antifungal; antioxidant; anticholinesterase	[33]
P. aleyreanum	Leaves, stems, aerial parts	Caryophyllene oxide; spathulenol; β-pinene; camphene; δ-elemene; β-elemene; β-caryophyllene; germacrene D; bicyclogermacrene	Antinociceptive; anti-inflammatory; gastric antiulcer; cytotoxic; antifungal; antioxidant; anticholinesterase	[33, 34]
P. aduncum	Fruits, leaves	β-pinene; E- caryophyllene; β-cubebene; β-elemene; α-copaene; α-farnesene; 1,8-cineole; α-terpineol; dillapiole	Larvicidal (*A. aegypti* L.); osmotic and morphologic fragility of erythrocytes; antihelmintic (*Haemonchus contortus*); Antiacarid (*Rhipicephalus* (Boophilus) *microplus*)	[35–38]
P. callosum	Leaves		Antifungal (*C. perniciosa*, *P. palmivora* and *P. capsici*)	[39]
P. cernuum	Branches	Camphene	Antitumoral	[21]
P. corcovadensis	Leaves	1-butyl-3, 4-methylenedioxybenzene; terpinolene; *trans*-caryophyllene; α-pinene	Larvicidal (*A. aegypti* L.)	[11]
P. diospyrifolium	Leaves	(*E*)-eudesma-6,11-diene; (*E*)-caryophyllene; γ-muurolene; limonene; germacrene; (*E*)-β-ocimene	Antifungal	[40]
P. enckea	Leaves		Antifungal (*C. perniciosa*, *P. palmivora* and *P. capsici)*	[39]
P. gaudichaudianum	Leaves	*E*-caryophyllene; α-humulene; bicyclogermacrene; *E*-nerolidol; viridiflorol; aromadendrene; β-selinene	Cytotoxic (*Saccharomyces cerevisiae*); larvicidal (*A. aegypti* L.)	[41]
P. hispidum	Aerial parts	δ-3-carene; limonene; α-copaene; β-caryophyllene; α-humulene; β-selinene; caryophyllene oxide	Cytotoxic; antifungal; antioxidant; anticholinesterase	[33]
P. hispidinervum	Leaves	Safrol; α-terpinolene	Antifungal (*B. sorokiniana*, *F. oxysporum* and *C. gloeosporioides)*; insecticidal (*S. frugiperda*); amoebicidal (*A. polyphaga*)	[24, 42, 43]
P. hostmanianum	Leaves	Asaricin; myristicin	Larvicidal (*A. aegypti* L.)	[44]
P. humaytanum	Leaves	*β*-selinene; caryophyllene oxide	Larvicidal (*A. aegypti* L.)	[44]
P. malacophyllum	Leaves	α-pinene; camphene; camphor; *E*-nerolidol	Antimicrobial; antifungal	[45]
P. marginatum	Leaves	Isoelemicin; Apiol; δ-guaiene	Antifungal (*C. perniciosa*, *P. palmivora* and *P. capsici)*; larvicidal (*A. aegypti* L.)	[35, 39]
P. nigrum	Seeds	Limonene; *E* caryophyllene; caryophyllene oxide	Larvicidal (*A. aegypti* L.)	[35]
P. permucronatum	Leaves	Dillapiol; myristicin	Larvicidal (*A. aegypti* L.)	[45]
P. vicosanum	Leaves	α-Alaskene; *Y*-elemene; limonene	Anti-inflammatory	[46]

Table 1. *Piper* species of Brazil with biological properties.

and γ-eudesmol (6.7%). The constituents with the greatest quantities in the oil obtained from the leaves of *Piper dilatatum* were (*Z*)-β-ocimene (19.6%), β-caryophyllene (11.3%), sesquiterpene (8.8%), bicyclogermacrene (8.8%), spathulenol (6.5%) and caryophyllene oxide (5.3%). The analysis of the essential oil of *P. hispidum* leaves revealed the presence of β-pinene (19.7%), α-pinene (9.0%), δ-3-carene (7.4%), α-cadinol (6.9%) and spathulenol (6.2%) as major compounds [50].

The analysis of the essential oil of *Piper* species of the Amazon revealed the presence of the sesquiterpenes α-copaene, (*E*)-caryophyllene and spathulenol in all species analyzed. The major compounds identified in *Piper amapense* oil were (*E*)-caryophyllene (25.0%), β-selinene (15.0%) and caryophyllene oxide (17.0%). The oil of *Piper duckei* had a predominance of (*E*)-caryophyllene (23.5%), caryophyllene oxide (18.4%), β-eudesmol (9.4%) and α-eudesmol (9.1%). The major volatile compounds found in *Piper bartlingianum* were α-cadinol (11.2%), β-elemene (10.5%), α-muurolol (9.4%) and (*E*)-nerolidol [51].

Analyses of the essential oils from the leaves, stems and flowers of *P. regnellii* collected in Dourados in the state of Mato Grosso do Sul revealed the presence of myrcene and anethole, with the major constituent in the stem being dillapiole. In the leaves, the main compounds were myrcene (21.9%), anethole (*E*) (16.0%) and bicyclogermacrene (9.4%). In the stem, they were anethole (*E*) (13.4%), dillapiole (30.4%) and myrcene (14.9%). For the flowers, they were anethole (*E*) (28.2%), myrcene (23.0%) and bicyclogermacrene (9.6%) [52].

5. Biological activities of essential oils of the *Piper* species from Brazil

Due to their complex chemical composition, essential oils show a range of pharmacological actions, making them potential sources for the development of new drugs [53].

The antimicrobial activity of essential oils, both *in vitro* and *in vivo*, has justified research on traditional medicine focused on the characterization of their antimicrobial activity [54]. The search for more effective antimicrobial agents has become a challenge for the medical field and has gained increasing importance. According to studies by Ref. [45], the essential oil of *Piper malacophyllum* collected in Florianopolis in the state of Santa Catarina showed significant antimicrobial activity, especially antifungal activity shown to be moderate against the *Cryptococcus neoformans* yeast and the *Trichophyton mentagrophytes* filamentous fungus, both of clinical interest. This activity is attributed to the synergism of the chemical constituents present in the essential oil.

Work done with essential oils obtained from medicinal plants has shown activity on plant pathogen control that could replace the use of pesticides, which, in the long term, cause negative impacts on society and the environment due to pollution from their chemical waste [55]. The essential oils of *P. callosum*, *P. marginatum* and *Piper enckea* collected in the state of Pará showed inhibitory activity against several pathogens, including *Crinipellis perniciosa*, *Phytophthora palmivora* and *Phytophthora capsici*. *P. callosum* caused 100% mycelial inhibition of *P. capsici* at a concentration of 0.75 μL/mL, the best fungitoxic action on the three pathogens tested [39]. The essential oil of *P. hispidinervum* inhibited growth of the *Bipolaris sorokiniana*, *Fusarium oxysporum* and *Colletotrichum gloeosporioides* pathogens, attributing the fungicidal effect observed in the essential oil to the presence of safrole (89%), its major component [42].

Ref. [43] evaluated the insecticidal activity of the essential oil of *P. hispidinervum*, collected in Lavras in the state of Minas Gerais, on *Spodoptera frugiperda* (Fall armyworm), attributing the effect to safrole (82%), the major component of the essential oil being analyzed. The essential oil of *Piper betle* showed insecticidal activity by inhibiting the development of *Spodoptera litura* pupae without causing damage to the *Eudrilus eugeniae* organism [56].

Ref. [33] reported anticholinesterase activity for the essential oils of *Piper anonifolium* and *P. hispidum* collected in Bahia, while the oil of *P. aleyreanum* showed high cytotoxic activity against melanoma. The oils of the three species of *Piper* analyzed showed strong antifungal activity against *Cladosporium sphaerospermum* and *Cladosporium cladosporioides*.

Essential oils from the fruits of *P. aduncum*, leaves of *P. marginatum* and seeds of *Piper nigrum*, collected in Paraíba, were tested against dengue mosquito larvae and were shown to be active. The *P. marginatum* species had the greatest larvicidal effect [35]. The essential oil of *P. corcovadensis* revealed a potent larvicidal activity against the oviposition of *Aedes aegypti* [11].

In a study conducted by Girola et al. [21], the monoterpene camphene isolated from essential oil of *P. cernuum*, collected in Cubatão in the state of São Paulo, induced apoptosis in melanoma cells, and showed antitumor activity *in vivo*, thus showing itself to be a promising compound in cancer therapy.

The essential oil of *Piper vicosanum* collected in the city of Dourados, in the state of Mato Grosso do Sul, demonstrated anti-inflammatory activity in rodents and did not cause acute toxicity or mutagenicity [46]. The essential oil of *P. aleyreanum* extracted from a specimen from Porto Velho in the state of Rondônia, showed antinociceptive action, as well as anti-inflammatory and gastroprotective properties with great potential for the development of phytomedicines [34].

The literature reports a wide range of essential oils from the *Piper* genus with different biological properties. The essential oil of *P. hispidinervum* collected in Porto Alegre, in the state of Rio Grande do Sul, showed amebicide action against the trophozoites of *Acanthamoeba polyphaga*, preventing its encysting. This suggests that this essential oil has the potential to develop new drugs to treat keratitis. It also demonstrated little toxic effect against Vero cells (renal cells of the African green monkey) and is not toxic at concentrations less than 0.25 mg/mL [24]. The essential oil of *Piper diospyrifolium* collected in Maringa, in the state of Parana, showed antifungal activity against *Candida albicans*, *Candida parapsilosis* and *Candida tropicalis* isolated from catheter urine, blood culture and orotracheal tube samples donated by the University Hospital of Maringá, demonstrating effective activity as a possible new phytotherapy or natural fungicide [40].

6. Conclusions and future perspectives

According to the literature, we can say that the essential oils from the *Piper* species of Brazil have many uses. In addition, they are endowed with interesting biological activities and have a therapeutic potential. For example, they exhibit antimicrobial, anticholinesterase, antitumor, anti-inflammatory activities and may be useful as natural remedies and it seems that they can be used as a suitable therapy for many pathologies. Therefore, economic importance of essential oils from the *Piper* species of Brazil is indisputable. It appears therefore imperative to preserve our natural, diverse flora and support its protection in order to keep this inexhaustible source of molecules destined for multiple targets.

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