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Ethnomedical uses and pharmacological activities of most prevalent species of genus *Piper* in Panama: A Review

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Abstract

Ethnopharmacogical relevance: Piperaceae is the fifth largest family of plants in Panama. This review focuses on the ethnomedical uses of the most prevalent Panamanian species and biological activities of their extracts and/or constituents both in Panama and worldwide. Many species have a plethora of ethnomedical uses such as antibacterial, antifungal, anti-inflammatory, anticancer, antidiabetic, anti-*Helicobacter pylori*, antiulcer, antiprotozoal, estrogenic, insecticidal, local anesthetic, diuretic, and for women's health conditions.

Aim of the review: The aim of this review is to compile all ethnomedical uses of most prevalent species of *Piper* in Panama, and their extracts or phytoconstituents worldwide, through a complete literature search, so that it may allow selection of potential unexplored *Piper* species for future research and development of phytotherapeuticals for important ailments.

Methodology: This review conducted a thorough search in books and databases such as Google Scholar, PubMed, Sci-Finder, Scopus, ACS publications, Science Direct, and Reaxys (Elsevier), until October of 2017. The information provided in this review is based on peer-reviewed papers only in English. The key words used to search were: "*Piper*, "Piperaceae," "Panama", "Pharmacological activity", "Chemistry," "Toxicity," and "Clinical studies". Scientific names of the plants were validated through *www.tropicos.org*. Potential full-texts of eligible papers, irrespective of database, were identified. Study selection and data extraction were conducted by one author (AIS) and confirmed by others (MPG, ADA). The extracted data were summarized in tabular form and a narrative description was used to provide a summary of updated information.

Results: The ethnomedical uses of most prevalent 23 Panamanian species of *Piper* both in Panama as well in the world are provided. Of these species only *Piper arboreum*, *Piper auritum*, *Piper cordulatum*, *Piper hispidum*, *Piper dariense*, *Piper multiplinervium* and *Piper umbellatum have* ethnomedical uses in Panama. Some of the uses are by native Amerindians of Panama. These

include ailments such as liver pains, common colds, skin infections, insecticidal, as a bath to alleviate colds, snakebites, different types of pains, skin ailments, wound healing, rheumatism, women's health, antipyretic, and anti-inflammatory. Other Panamanian species are widely used in many countries of the world. Of all the *Piper* species, *P. aduncum* has the most ethnomedical uses. Panamanian uses are different from the ones in other countries. A total of 61 compounds present in *Piper* species reported in this review have shown a variety of biological activities *in vitro.* These compounds belong to different chemical types, such as chromenes, amides, alkaloids, benzopyrans, benzoates, essential oils, pyrrolidines, flavokaines, chalcones, methylenedioxy propiophenones, cinnamates, monoterpenes, sesquiterpenes, phenols, among others. From this review it is evident that extracts and pure compounds isolated from P*iper* species have shown a wide array of mainly *in vitro* activity and some ethnomedical uses may be correlated with their activities reported.

Conclusions: Plants of this genus have provided bioactive species, both from crude extracts and pure compounds thus substantiating their efficacy in traditional medicine. *In vivo* and toxicological studies are still limited, but the results of different activities of *Piper* reported point out the great potential of these species for obtaining bioactive principles that may be useful in treating diseases. However, a thorough investigation of *Piper* species relating to chemistry, *in vivo* pharmacological activities, with emphasis on their mechanism of action, safety and efficacy and toxicity is warranted.

Abbreviations:

ED_{50}: Effective dose concentration; **GI_{100}:** 100% growth inhibition; **IC_{50}:** Half maximal inhibitory concentration; **LC_{50}:** 50% Lethal concentration; **MIC:** Minimum inhibitory concentration; **MAR:** Maximum amount required

Keywords: *Piper* spp.; Ethnomedicine; Genus *Piper*; Panama; Chemistry; Pharmacology; Toxicology.

1. Introduction

The genus *Piper* belongs to the family Piperaceae composed of about 1,000 species. Approximately 300 *Piper* species are distributed in the tropical regions of Asia and Oceania; while two species are endemic to Africa. Nevertheless, the largest diversity of species is found in the Neotropics (Dyer and Palmer, 2004). Piperaceae consists mainly of herbs (terrestrial and epiphytes), shrubs, vines or trees and includes six genera and at least 3000 species in the world, usually with aromatic scents due to the volatile oils and usually containing alkaloids. These species are usually distributed in the tropics and subtropical regions (Mabberley, 1997; Judd et al., 2008; Simpson, 2010). Piperaceae is one of the largest families of plants in Panama, occupying fifth place in Panamanian Flora. Its medical potential has not been explored. This initially invited review was to form part of special supplement of *Journal of Ethnopharmacology* on Ethnobotany of Mesoamerica. Unfortunately, because of reasons beyond control it was not completed. We have now completed the review and are submitting now for publication in a regular volume of the Journal. This should be great interest for the scientists in the Neotropics who may be interested in studying Piperaceae species of their countries. A common description for Piperaceae taxon includes spiral-leaves, simple stipulate or not. The inflorescence is a spike or spadix with minute flowers uni- or bisexual, bracteate, perianth absent (flowers naked without sepals or petals). The flowers are only present a single pistil and stamens (Mabberley, 1997; Judd et al., 2008; Sympson, 2010). In Panama, three genera of Piperaceae and 200 species are reported, with genus *Piper* covering 59.5% (137 species),

Peperomia 40% (80 species) and *Manekia* 0.5% (1 species). The majority of the species are found in lowlands between 0 – 2000 m height (Correa, 2016). Fifty per cent of the genera are represented in the country, of which 33% are endemic. Some species are used locally, especially by the Amerindians of Panama for ethno-medicinal purposes.

Almost all *Piper* species are aromatic, due to the presence of oil cells in their structures (Dyer and Palmer, 2004). The use of plants and their extracts as remedies for treating a plethora of health conditions represents an ancestral legacy among many cultures in the world. In light of this the World Health Organization (WHO) has highlighted the significance of the traditional medicine, which include the use of plants (Roersch, 2010). The leaves, flowers and other parts of *Piper* species are used *inter alia* in treatment of gastrointestinal diseases, hypertension, women's health conditions, anti-hemorrhagic, diuretic, pains and inflammation (Dominguez et al., 1986; Gupta et al., 1993; De Filipps et al., 2004; Reigada et al., 2007; Roersch, 2010; da Silva et al., 2014; Novaes et al., 2014). A variety of natural products having different pharmacological properties have been identified in plants of the genus *Piper* (Orjala et al., 1993; Navickiene et al., 2000; De Leon et al., 2002; Parra et al., 2011; Carrara et al., 2013; Iwamoto et al., 2015).

A diversity of scientific reviews on species of the genus *Piper* have been published (Roersch, 2010; Gutierrez et al., 2013; Monzote et al., 2017). For more than forty five years we have been interested in investigating the pharmacological potential of the Panamanian rich biodiversity for treatment of diseases. *Piper* species are nonetheless among the most significant plants of our interest. In Panama the traditional practices that include the use of *Piper* species to treat a diversity of illnesses are associated with the "*Gunas*"culture (earlier named Kunas) (Gupta et al., 1993). This review describes the ethnomedical uses and

pharmacological activities of plants of the genus *Piper*, or their constituents, which occur in Panama. The information provided in this review will be of value not only for the discovery of new drugs with pharmacological use, but also for the development and promotion of national health strategies that consider the use of the traditional medicine within the system.

2. Material and methods

The present review paper considered the literature published prior to October 2017 on ethnomedical uses, pharmacology and toxicity of extracts, essential oils and natural products isolated from different parts of *Piper* species found in Panama. Therefore, only literature available in books and databases such as Google Scholar, PubMed, SciFinder, Scopus, ACS publications and Science Direct was reviewed. This review only considered peer-reviewed research papers with impact factor.

Scientific names were validated through www.tropicos.org. The keywords used to search were: anti-cancer, anti-inflammatory, antimicrobial, antiulcer, chemistry, insecticidal, pharmacological activity, Panama, *Piper*, Piperaceae, and traditional uses.

3. Ethnomedical uses

The ethnomedical uses of different species of *Piper* found in Panama have been documented in tropical countries of America, Africa, Asia and Oceania. In Table 1, the ethnomedical uses of most prevalent 23 species of *Piper* , namely *P. aduncum, P. amalago, P. arboreum, P. arboretum, P. auritum, P. bogotense, P. bremedeyeri, P. cordulatum, P. crassinervium, P. cumanense, P. darienensis, P. dilatatum, P. fimbriulatum, P. hispidum, P. jacquemontianum, P. lanceaefolium, P. longispicum, P. marginatum, P. multiplinervium,*

P. obliquum, P. peltatum, P. septuplinervium, P.tuberculatum, and *P. umbellatum* are reported including the disease state, plant part used and the countries (or geographic regions).

Ethnomedical uses of *Piper aduncum* are recorded in four countries of Latin America (Brazil, Colombia, Honduras and Peru), in Indonesia and in Papua New Guinea. In Papuan folk medicine, the extract of the leaves of *Piper aduncum* is used to treat insect bites, dressing sores and cuts, and scabies. Extracts of the bark are used for the treatment of toothache, diarrhea, dysentery, scabies, cuts, cough and fungal infections (Siges et al., 2005). On the other hand, the roots are used to treat stomach and respiratory ailments, skin wounds and dysentery; while extracts of the stem and fruits are used for treating headache and toothache, respectively (Siges et al., 2005). *P. aduncum* is used in the traditional medicine of Indonesia to treat burns (Lohézic-Le Dévéhat et al., 2002). In Peru the extracts of *P. aduncum* are used for treatment of diarrhea; while the aerial parts are applied against rheumatic afflictions, and as an astringent, styptic and antiseptic (Macedo and Oviedo, 1987; Kloucek et al., 2005). The *Yaneshas*, original inhabitants from the Peruvian Amazon, prepare teas and steam baths from the leaves for general infections and fever (Valadeau et al., 2009). In Colombia, extracts of the plant are used to treat dysentery and haemostasis (Diaz et al., 1984). The plant is used in the Brazilian folk medicine to treat diseases of the digestive tract, flu and as an insect repellent (Potzernheim et al., 2012). In the Brazilian Amazonia the leaves of *P. aduncum* are used for treatment of intestinal and stomach ailments (Vandenberg, 1993). The leaves of *P. aduncum* are used for treating erysipelas, cystitis, gynecological inflammation, disorders of the digestive tract, wound healing and pyelitis (Vieira, 1991; Vandenberg, 1993; Coimbra, 1994; De Almeida et al., 2009). In the

Amazon region the leaves and fruits of this plant are used as antimycotic, antimicrobial and styptic (Schultes and Raffauf, 1990). The leaves, fruits and stems of *P. aduncum* are used by the native cultures of Honduras for treatment of female disorders, pains, as digestive and skin cleanser (Lentz et al., 1998).

Piper amalago is used in popular medicine as an anti-inflammatory, antipyretic, analgesic, vermifuge, and for treatment of stomach problems (Parmar et al., 1997; Carrara et al., 2013). In Mexico, this plant is used in the Huasteco-Maya folk medicine against edema, inflamations and as an antipyretic. The leaves are also used for treatment of headache, nosebleed, pains, sores, and to prevent miscarriage. Its bark is used to treat cough, gastrointestinal and chest pains. The tender shoots are applied for treating vertigo problems (Domínguez and Alcorn, 1985; Dominguez et al., 1986).

In Brazil, *P. amalago* is used in the popular medicine as diuretic, for treating hypertension and renal calculi. The leaves are used to prepare a tea that is used for treating burns (Alves et al., 2008; Novaes et al., 2014).

Traditionally, a decoction of *Piper arboreum* is used in the Brazilian traditional medicine to treat sexually transmitted diseases, bronchitis, urinary infections, rheumatic problems and as carminative. In the folk medicine of Northeast of Brazil the plant is used as sedative and to counteract the effects of snakes bites (Bezerra et al., 2007; De S. Luna et al., 2005; Regasini et al., 2009; Tintino et al., 2014). The inflorescense of *P. arboreum* is used to prepare a remedy for treatment of hepatic pains; while a decoction obtained from the leaves is drunk to treat the same condition (Gupta et al., 1993).

Piper auritum is used for treatment of different medical conditions. It is used as diuretic, antipyretic, for gout, angina, erysipelas, venereal diseases, colic, and headache. The plant is

also used as an appetite stimulant, local anesthetic, and wound poultice (Monzote et al., 2010). *P. auritum* has different uses in North and Central American countries. In Mexico, the "*Chinantec*" group uses the leaves to make a decoction, which is drunk to facilitate childbirth and as an emmenagogue (Browner, 1985); while the plant is used in the "*Mayan*" traditional medicine for healing wounds (Caamal-Fuentes et al., 2011). The plant is used in Guatemala for treatment of dysmenorrhea and as galactagogue (Michel et al., 2007). In El Salvador, a juice prepared from the leaves is applied to remove ticks (Schultes, 1975). The fresh leaves of *P. auritum* are used in the folk medicine of Costa Rica to treat headaches (Tucker and Maciarello, 1998). From the inflorescence of *P. auritum*, the Panamanian natives "*Gunas*" prepare an infusion that is drunk to treat common colds (Gupta et al., 1993).

Coe (2008) reported the use of Piperaceae in the "*Rama*" traditional medicine of Nicaragua. *P. aduncum, P. amalago, P. auritum, P. hispidum, P. jacquemontianum, P. peltatum* and *P. tuberculatum* have been extensively used as remedy for a large number of conditions that affect women and infants. In South America the leaves are macerated and used by natives of the region of Antioquia (Colombia) against snakebites (Vásquez et al., 2013).

Traditionally, the Panamanian endemic plant *P. cordulatum* has been used as a remedy for skin infections (Roming et al., 1992).

The medicinal uses of *Piper hispidum* have been reported in Latin American traditional medicine in Brazil, Colombia, Ecuador, Guatemala, Honduras, Mexico, Panama and Peru, for the treatment of different health problems. In Brazil, a leaf infusion is drunk as anti-hemorrhagic and diuretic (da Silva et al., 2014). In the Colombian folk medicine a leaf

decoction is used for treating malaria (Friedrich et al., 2005). The leaves of *P. hispidum* are used by the "Q'eqchi Maya" from Guatemala for the treatment of female diseases (Michel et al., 2007). Furthermore, the leaves are used in Nicaragua as a remedy to ease the pain of childbirth, anemia, and rheumatism (Michel et al., 2007). The plant infusion in Ecuador is applied to kill head lice (Schultes, 1975). In the Panamanian popular medicine, a leaf decoction of *P. hispidum* is used to treat conjunctivitis, diarrhea and hemorrhages. On the other hand, the inflorescence is applied topically for muscle aches (Gupta et al., 1993). The Mexican ethnic group "*Totonacs*" uses the fresh leaves externally for treatment of mumps and tonsillitis (Martinez, 1984). In Peru, the Amazonian ethnic group "*Chayahuitas*" apply the crushed leaves on the skin to treat leishmaniasis and for cicatrization of wounds (Estevez et al., 2007). Moreover, the leaf is used for prevention of tooth decay (Lewis and Elvin-Lewis, 1984). In Honduras, the plant is used for treatment of insect and snake bites, and as a skin cleanser (Lentz et al., 1998). In Jamaica, *P. aduncum* and *P. hispidum* are used for stomach aches and colds (Burke and Nair, 1986).

The Guna Indians (formerly called Kuna Indians) of Panama use the decoction of *Piper darienensis* C. DC, called "*Duerme boca*" and "*kana*" as bath to alleviate cold and to treat snakebites (Duke 1975). The Chocó Indians of Panama use this plant as an effective remedy for treating toothaches and as a fish poison. (Duke 1970)

In French Guyana, a preparation is made from the leaves of *Piper marginatum* for the treatment of malaria (Vigneron et al., 2005). In Brazilian folk medicine the plant is used as an antidote for snake bites, as antispasmodic, carminative, antispasmodic, diuretic, for blood pressure control, for treatment of asthma, erysipela, problems of the urinary system, vesicle and liver diseases (De Oliveira Chaves and De Oliveira Santos, 2002; de

Albuquerque et al., 2007; Reigada et al., 2007). In Trinidad and Tobago, Puerto Rico and Surinam this species has been used to treat female disorders and to help during childbirth (Bru and Guzman, 2016).

Gupta et al. (1993) reported the traditional use of an infusion prepared from young leaves of *Piper multiplinervium*, by the "*Gunas*" Amerindians, which is drunk for treating different types of pains.

In Ecuador, *Piper obliquum* is used by the "*Ketchwa*" Indians to treat dental problems. The stem of the plant is used in the folk medicine of French Guyana as a remedy for hernia; while in Guyana, the "*Patamona Amerindians*" use the warmed leaves for treating pains, muscular aches and for arthritis (DeFilipps et al., 2004).

Pinto et al. (2010) described the use of infusions of leaves and roots of *P. peltatum* in the traditional medicine of Brazil for treatment of erysipela, malaria, leishmaniasis and hepatitis.

The traditional medicinal uses of *Piper umbellatum* have been reported in 24 countries of the tropical regions of Africa, Asia and Latin America (Roersch, 2010). Roersch (2010) has reviewed the ethnomedical uses of *P. umbellatum* in 24 countries of the world and pointed out the uses of different plant parts, applied in different manners (decoctions, infusions, maceration, teas, etc) for the treatment of the urinary tract infections, skin and liver ailments , contusions, digestive problems, pains, wound healing, swelling, rheumatism, women's diseases, as antipyretic and anti-inflammatory. Moreover, different pharmacological activities of the pure compounds and extracts obtained from *P. umbellatum* at the date of publication of this review are also covered.

4. Pharmacological activity

4.1. Antimicrobial activity

Orjala et al. (1989) evaluated *in vitro* antibacterial and antifungal activities of the crude petroleum ether extract of *P. aduncum*. The extract exhibited a strong antibacterial activity against *B. subtilis*, *E. coli*, and *M. luteus*, but a weak antifungal activity on *P. oxalicum*. Four compounds isolated from this extract, methyl 8-hydroxy-2,2-dimethyl-2*H*-chromene-6-carboxylate (**1**), 2,2dimethyl-8-(3-methyl-2-butenyl)-2*H*-chromene-6-carboxylic acid (**2**), methyl 3-(6- hydroxy-3,7-dimethyl-2,7-octadienyl)-4-methoxy-benzoate (**3**), and methyl 3-(2-hydroxy-3-methyl-3-butenyl)-4-hydroxybenzoate (**4**) were found to be active against *E. coli*, *M. luteus*, *B. subtilis*, and *P. oxalicum* (Orjala et al., 1993). Compound **1** was active against all strains tested (MIC = 8.5-17 nmol). On the other hand, compound **2** was active against all strains except *E. coli* (MIC = 3.2-15.5 nmol); while compound **3** was active against *M. luteus* and *B. subtilis* with a MIC of 10.8 nmol; and compound **4** displayed activity against *M. luteus* (MIC of 6.6 nmol) and *B. subtilis* (MIC of 13.0 nmol). Bioautographic assays on TLC plates used for detection of antimycotic activity of the chloroform (branch) and aqueous (leaves) extracts from *P. auritum*, collected in Panama, revealed activity against *C. albicans* at 50 µg (Rahalison et al., 1993).

Navickiene et al. (2000) assessed the antifungal activity of ten amides isolated from the chloroform extract of the stems, and the dicloromethane:methanol extract of the seeds of *P. hispidum* and *P. tuberculatum* respectively, by bioassay-guided fractionation against *Cladosporium sphaerospermum*. (3Z,5Z)-N-isobutyl-8-(3',4'-methylenedioxyphenyl)-heptadienamide (**5**), N-[3-(6'-methoxy-3',4'-methylenedioxyphenyl)-2(Z)-propenoyl]pyrrolidine (**6**) and piperamine (**7**), isolated from *P. hispidum*, exhibited similar

antifungal activity (minimum amount required for inhibition, MAR, of 5 µg). Moreover, two compounds, N-(12,13,14-trimethoxydihydrocinnamoyl)- Δ^3-pyridin-2-one (**8**) (MAR of 0.1 µg), and piperine (**9**) (MAR of 1 µg) isolated from *P. tuberculatum* exhibited potent antimycotic activity; whereas 8(*Z*)-N-(12,13,14-trimethoxycinnamoyl)-Δ^3-pyridin-2-one (**10**), piplartine (**11**), $\Delta^{\alpha,\beta}$ dihydropiperine (**12**), 5,6-dihydropiperlonguminine (**13**) and pellitorine (**14**) exhibited the same activity (MAR of 5 µg). This same group also reported that **11**, **12**, **14** and *cis*-piplartine (**15**) showed activity against *C. cladosporioides* at MAR of 5 µg (Vasques et al., 2002). The dicloromethane:methanol extract of the leaves of *P. tuberculatum* yielded fagaramide (**16**) (MAR of 5 µg), and two cinnamoyl derivatives: *trans*-6,7,8-trimethoxycinnamate (**17**) (MAR, 5 µg) and methyl 6,7,8-trimethoxydihydrocinnamate (**18**) (MAR, 10 µg), with activity against this fungus (Vasques et al., 2002). In addition, four compounds obtained from the dried leaves of *P. arboreum* revealed activity against *C. sphaerospermum* (Vasques et al., 2002). N-[10- (13,14-methylenedioxyphenyl)-7(E)-pentaenoyl]-pyrrolidine (**19**) and N-[10-(13,14-methylenedioxyphenyl)-7(E),9(E)-pentadienoyl]-pyrrolidine (**20**) showed equipotent activity (MAR of 0.1 µg), stronger than the antifungal control miconazole (MAR of 0.5 µg); whereas N-[10-(13,14-methylenedioxyphenyl)-7(*E*),9(*Z*)-pentadienoyl]-pyrrolidine (2**1**) and arboreumine (**22**) showed antifungal activity of 10 and 5 µg respectively.

By fractionation of the methanol extract obtained from the leaves of *P. lanceaefolium*, López et al., (2002) isolated lanceafolic acid methyl ester (**23**) and pinocembrin chalcone (**24**), which were evaluated on *C. albicans*. Both compounds showed activity against the fungus with a MIC of 100 µg/mL.

The antifungal activity of compounds isolated from the EtOAc and methanol extracts of the leaves of *P. crassinervium*, and from the hexane and dicloromethane leaves' extracts of *P. aduncum* were evaluated *in vitro* against *C. cladosporioides* and *C. sphaerospermum* (Danelutte et al., 2003;Lago et al., 2004). *P. crassinervium* yielded 7 compounds, crassinervic acid (**25**), 4-hydroxy-(3′,7′-dimethyl-1′- oxo-octa-2′-E-6′-dienyl) benzoic acid (**26**), 4-hydroxy- (3′,7′-dimethyl-1′-oxo-octa-2′-Z-6′-dienyl)benzoic acid (**27**), 3,4,5-trimethoxydihydrocinnamic acid (**28**), 1,4-dihydroxy- 2-(3′,7′-dimethyl-1′-oxo-octa-2′-E-6′-dienyl) benzene (**29**), naringenin 4′-methyl ether (**30**) and sakuranetin (**31**), which showed antifungal activity on both fungi with MIC between 0.5 and 10 µg. The 4-hydroxybenzoic acid, compound **25**, showed the highest activity (MIC of 0.5 µg) against both fungi. Further, five compounds isolated from the extracts of *P. aduncum*, aduncumene (**32**), methyl 2,2-dimethyl-8-(3′-methyl-2′-butenyl)- 2*H*-1-benzopyran-6-carboxylate (**33**), methyl 2,2-dimeth- yl-2*H*-1-benzopyran-6-carboxylate (**34**), methyl 8-hydroxy- 2,2-dimethyl-2*H*-1-benzopyran-6-carboxylate (**35**) and 2,2-dimethyl-2*H*-1-benzopyran-6-carboxylic acid (**36**), revealed antifungal activity against *C. cladosporioides* and *C. sphaerospermum* (MIC range 0.1-5 µg). Compound **33** had the highest antifungal activity against both fungi (MIC of 0.1 µg). Furthermore, bioassay-guided fractionation of the ethanol extract obtained from the leaves of *P. aduncum* led to the identification of prenylated methyl benzoates, two chromenes and one flavanone, whose antimycotic activities were evaluated by the same research group against *C. cladosporioides* and *C. sphaerospermum* (Lago et al., 2009). Methyl 4-hydroxy-3-(2'-hydroperoxy-3'-methyl-3'-butenyl) benzoate (**37**), methyl 4-hydroxy-3-(3'-methyl-2'-butenyl) benzoate (**38**), and pinocembrin (**39**) exhibited the same activity than the antifungals nystatin and miconazole

(MAR of 1 µg), while the activity of methyl- 4-hydroxy-3-(2'-hydroxy-3'-methyl-3'-butenyl) benzoate (**40**), methyl 2,2-dimethyl-2*H*- 1-benzopyran-6-carboxylate (**41**) and compound **35** were 5-fold less active than the positive antifungal controls.

Navickiene et al. (2006) reported that the essential oil obtained from the fruits of *P. aduncum* and *P. tuberculatum* had a high activity against *Cladosporium cladosporioides* (MIC = 10 µg, fruits) and *Cladosporium sphaerospermum* (MIC = 10 µg, fruits), respectively.

The prenylated salicylic acid derivative, 3-farnesyl-2-hydroxy benzoic acid (**42**), isolated from the leaves of *P. multiplinervium* exerted antimicrobial activity against *S. aureus, K. pneumoniae, M. smegmatis,* and *P. aeruginosa* and *H. pylori* with an MIC between 6.25 and 12.5 µg/mL (Rüegg et al., 2006). This compound also showed anti-*Helicobacter pylori* activity (MIC of 3.75 µg/mL) that might explain its use by the Guna Indians of Panama to treat stomachaches.

In antifungal assays, the methanol extract obtained from the leaves of *P. aduncum* inhibited moderately the growth of *C. albicans* (MIC of 1.25 mg/mL) (Braga et al., 2007).

Bioassay guided fractionation of the methanol fraction from the dried leaves of *P. marginatum* afforded two flavanones, compound **31** and 5,7-dihydroxy-4'-methoxyflavanone (**43**), with an important antifungal activity against *C. cladosporioides* and *C. sphaerospermum*. The activity of both compounds was similar for both species (MIC = 1.0 µg) compared to the antifungal controls (nystatin and miconazole) (Reigada et al., 2007). Furthermore, other three compounds isolated from these extracts, 3,4-methylenedioxypropiophenone (**44**) (MIC of 5.0 µg for both strains), 2-methoxy-4,5-

methylenedioxypropiophenone (**45**) (MIC of 5.0 µg for both strains), and 1-(3,4-methylenedioxyphenyl)propan-1-ol (**46**) (MIC of 10 µg for both strains), showed antimycotic activity. The more potent activity of the flavanones were attributed to the presence of the carbonyl group in both compounds.

The methanol extract obtained from the leaves of *P. crassinervium* showed a strong fungitoxic potential (Lago and Kato, 2007). The antifungal activity of the piperidone derivative 3α, 4α -epoxy-2-piperidone (**47**), isolated from this extract, showed the same MIC (1 µg) against *C. cladosporoides* and *C. sphaerospermum*, which was similar to that observed for the antifungals controls nystatin and miconazole. Da Silva et al. (2014) reported that *P. hispidum* essential oil showed a strong activity against both fungi, with a detection limit of 0.1 µg and 1 µg for *C. cladosporioides* and *C. sphaerospermum*, respectively.

From the ethanolic extract of *P. obliquum* inflorescences two compounds with high antibacterial activity were isolated, obliquol A (**48**) and obliquol B (**49**) (Valdivia et al., 2008). Compound **48** showed MIC values of 5.0 and 2.5 µg/mL for *E. coli* and *Staphylococcus epidermis* respectively; while **49** exhibited a MIC of 5.0 µg/mL.

Palacios et al. (2009) reported that the diclorometh ane:methanol, ethanol extracts and decoction from the inflorescence and leaves of *P. tuberculatum* completely inhibited the growth of the dermatophytic fungus *Trichophyton rubrum* at concentrations at 100 and 500 µg /mL.

The ethanol extract obtained from the leaves of *P. arboreum* inhibited strongly the growth of the opportunistic fungus *Candida krusei* (MIC of 62.5 µg /mL) (Regasini et al., 2009a). Three compounds isolated from this extract, piperyline (**50**), 4,5-dihydropiperyline (**51**) and

tetrahydropiperyline (**52**) showed a strong antifungal activity on *C. krusei* and *C. parapsilosis* (MIC between 15.6 and 31.2 µg /mL). Furthermore, **51** and **52** displayed a potent antifungal activity against *C. neoformans*, with a MIC of 31.2 and 15.6 µg /mL, respectively. The strongest activity of compound **52** could be due the lack of double bonds in its chemical structure.

By using the micro-dilution method Morandim-Giannetti et al. (2010) showed that the essential oil of *P. aduncum, P. crassinervium,* and *P. tuberculatum* have antifungal activity. *P. aduncum* had the highest antifungal activity against *Cryptococcus neoformans* (MIC of 62.5 µg/mL), while the essential oils of *P. crassinervium,* and *P. tuberculatum* showed a moderate activity against *Candida albicans*, *C. krusei*, *C. neoformans* and *C. parapsilosis* (MIC > 250 µg/mL, and > 1000 µg/mL, respectively).

From the aerial parts of *P. cumanense* , Parra et al. (2011) isolated the cumanensic acid (**53**), that showed antifungal activity against *Botrytis cinerea* (MIC of 100 µg) and *Fusarium oxysporum* (MIC of 1 µg) similar to the standard control benomyl. Furthermore, they also isolated cumenic acid (**54**) from the inflorescences of the plant, which showed antifungal activity on the same fungi studied, with a MIC of 10 µg and 1 µg, respectively.

The diclorometh ane extract of the roots of *P. dilatatum* exerted antifungal activity on *C. cladosporioides* and *C. sphaerospermum* at MIC of 200 µg for both strains (dos Santos et al., 2013). The major component isolated from the extract, (+)-(7S,8R)-epoxy-5,6-didehydrokavain (**55**), displayed a strong antifungal activity with a MIC 1 of µg for both fungal strains, followed by flavokavain B (**56**) (MIC of 100 µg).

The essential oil of *P. aduncum* showed bactericidal activity against multridrug-resistant (MDR) and standard strains of *Staphylococcus spp* (Brazao et al., 2014). The oil was more active against *S. aureus* and *S. epidermidis* standard strains (MIC of 500 and 250 μg/mL respectively). The authors suggested that the observed activity could be due to the synergistic action of different components of the essential oil, such as piperitone (**57**) and myristicin (**58**).

The essential oils of *P. hispidum*, *P. bremedeyeri*, *P. bogotense* and *P. marginatum* showed strong activity against *Trichophyton rubrum* and *T. mentagrophytes* (MIC range, 79-500 μg/mL), which are important agents of dermatophytosis (Tangarife-Castaño et al., 2014). Moreover, the essential oils of *P. bogotense* and *P. hispidum* showed the highest activity against *T. rubrum* (MIC of 79 and 99 μg/mL, respectively); while the essential oil of *P. hispidum* exhibited the highest activity against the multi-resistant *Fusarium oxysorum*, which is a common etiological agent for onychomycosis (MIC of 500 μg/mL). Guerrini et al. (2009) have reported the complete *in vitro* inhibition of *T. mentagrophytes* and *T. tonsurans* after treatment with the essential oil of *P. aduncum* at a concentration of 500 μg/mL.

The hydroethanol extract of leaves of *P. umbellatum* were evaluated against Gram positive and Gram negative bacteria (da Silva et al., 2014). This extract was more active against *Salmonella typhimurium*, *Shigella flexneri* and *Enterococcus faecalis* with an MIC of 12.5 μg/mL for all bacterial strains. The mode of action of the extract is related to the changes in the membrane permeability of bacterial membrane and cell wall, which the authors attributed, in part, to the presence of flavonoids in the extract, mainly the antibacterial rutin (**59**) and quercetin (**60**).

In one study, the antimicrobial effects of the hydroalcoholic extract from the leaves *P. hispidum*, and three chalcones isolated from the same matrix were evaluated against *S. aureus* and *C. albicans* (Costa et al., 2016). The chalcones were chemically identified as 2'-hydroxy-4,4',6'-trimethoxy-chalcone (**61**); 2'-hydroxy-3,4,4',6'-tetrame-thoxychalcone (**62**) and 3,2'-dihydroxy-4,4',6'- trimethoxychalcone (**63**). The crude extract was active against *S. aureus* and *C. albicans* with a MIC of 62.5 µg/mL for each microorganism. Furthermore, **61** and **63** showed activity against *S. aureus*, both with a MIC of 125 µg/mL, while **62** exhibited an activity against the same strain at a MIC of 250 µg/mL. On the other hand, **61** and **63** inhibited the growth of *C. albicans* at a MIC of 250 µg/mL; while **63** was active against this fungus at a MIC of 500 µg/mL. In order to obtain more insights on the mechanism by which the extract of *P. hispidum* exerts its bioactivity the anti-biofilm effect of the extract and scanning electron microscopy studies were performed (Costa et al., 2016). The BIC_{50} (concentration that decreases 50% of the viability of the biofilms) of the extract was 200 µg/mL against *S. aureus*; and 70 µg/mL against *C. albicans*, showing to be more effective than the antifungal fluconazole (The BIC_{50} = >1000). The scanning electron microscopy studies revealed that at a concentration of the extract above 125 µg/mL the cells of *C. albicans*, exhibited changes, reduction of the formation of pseudohyphae, and in the number of cells compared with the controls.

4.2. Anticancer and anti-inflammatory activities

The process of tumor development, which includes initiation, promotion, malignant conversion and metastasis is largely influenced by the inflammatory responses

(Grivennikov et al., 2010). Thus, the discovery of new natural products with anti-inflammatory activity is required for cancer treatment.

De Leon et al. (2002), reported that the compound diayangambin (**64**), isolated from the leaves of *P. fimbriulatum* reduced ear swelling in mice when the compound (40mg/kg) was administrated orally to mice treated with 2,4-dinitrofluorobenzene. The reduction of swelling was related with the decrease in leukocyte infiltration. Moreover, in the carrageenan induced mouse paw-edema model, diayangambin significantly suppressed inflamed paw volume, and reduced *in vitro* the production of prostaglandin E_2 (40.8%) at a concentration of 10 μM.

The chloroform extract of the leaves of *P. amalago* revealed topical anti-inflammatory activity against the croton oil-induced ear oedema in mice with an ID_{50} of 498 μg/cm^2 (Sosa et al., 2002). The authors suggested that the presence of piperine-like amides and sesquiterpenes could explain the anti-inflammatory activity.

Valdivia et al. (2008) reported that compound **49** isolated from *P. obliquum* inflorescences strongly reduces the NF-κB activity in a dose-dependent manner, which might explain the anti-inflammatory activity of this compound.

Parise-Filho et al. (2011) investigated the anti-inflammatory activity of dillapiole (**65**), a natural compound present in high levels in the essential oil obtained from the leaves of *P. aduncum*. The anti-inflammatory activity was studied by carrageenan-induced edema in the rat´s paws. Compound **65** showed a good anti-inflammatory activity (17%) compared to indomethacin. The structure-activity study demonstrated that the alkyl groups in the side chain, the methoxy group in the aromatic ring and the benzodioxole ring are important for the observed bioactivity.

Among *Pieraceae* species, *P. umbellatum* revealed antiproliferative activity *in vitro* and *in vivo* (Iwamoto et al., 2015). Iwamoto et al. (2015) reported that the dichloromethane extract of the *P. umbellatum* fresh leaves inhibited inflammation in a dose independent manner. According to these authors, that in the first step of inflammation the extract acts on prostaglandins production due to the presence of sitosterols (**66**) and 4-nerolidylcatechol (**67**); subsequently, in second step of inflammation the extract produces an effect similar to corticosteroids on neutrophil mobilization, which effectively reduces the cellular phase of inflammation.

Furthermore, this extract inhibited the growth of melanoma, glioma, lung, prostate, kidney and ovarian human tumor *in vitro* cell lines (GI_{100} between 6.8 and 14.9 µg/mL). The observed anticancer effect was partially attributed to 4-nerolidylcatechol, *β*-sitosterol, campesterol (**68**), stigmasterol (**69**), and compounds **66** – **67,** which are present in the dichloromethane extract. The extract also showed *in vivo* antitumor activity by reducing Ehrlich solid tumor growth between 38.7 and 52.2% after oral daily treatments with 200 and 400mg/kg of the dichloromethane extract of *P. umbellatum*.

4.3. Antidiabetic activity

Gutierrez (2012) investigated the antidiabetic activity of fresh leaves of *P. auritum* in streptozotocin-induced type 1 diabetic rats. The hexane extract significantly decreased the blood glucose levels. The administration of 200 and 400 mg/kg of the extract increased serum and pancreatic tissue insulin. Moreover, the extract improved the activity of β-cells when compared with the controls. Furthermore, the hexane extract protected pancreatic beta cells from oxidative stress and from advanced glycation.

4.4. Antiulcer and gastric antisecretory effects

According to Burci et al. (2013), the fruits of *P. tuberculatum* have been used in the traditional medicine for treatment of digestive disorders. Based on this report they studied the gastroprotective and antisecretory activities *in vivo* of the dichloromethane fraction obtained from the fruit of *P. tuberculatum*, and compound **11**, a compound isolated from this fraction. By using rats with gastric ulcers induced by ethanol, oral treatment of animals with the dichloromethane fraction produced a reduction in the lesioned area of the gastric mucosa with an ED50 of 29 mg/kg. Also, the intraperitoneal administration at 1, 3 and 10 mg/kg, reduced gastric lesions. Treatment with **11** inhibited gastric ulcers by 80% at a dose of 4.5 mg/kg. This effect could be associated with the maintenance of the levels of GSH in the gastric mucosa. The diclorometh ane fraction also stimulated mucus secretion. Both, the dichloromethane fraction and **11** inhibited the H^+K^+-ATPase activity *in vitro*, and reduced basal gastric acid secretion *in vivo* promoting gastroprotection through a decrease in gastric acid.

The *in vivo* gastroprotective activity of the hydroethanolic extract of *P. umbellatum* was assessed in mice with induced gastric ulcer (da Silva et al., 2016). The extract reduced gastric lesions at 30, 100 and 300 mg/kg in a dose not dependent way. This activity was to a certain extent attributed to the antioxidant activity of the extract. Moreover, the anti-inflammatory, antisecretory and regeneration of the gastric mucosa was induced partially due to the antiulcer mechanism of action.

4.5. Antiparasitic Activity

2',6'-Dihydroxy-4'-methoxychalcone (DMC) (**70**) isolated from the dichloromethane extract from the inflorescences of *P. aduncum* proved to have a significant activity against

promastigotes and amastigotes form of *Leishmania amazonensis*, with a ED_{50} of 0.5 and 24 µg/mL, respectively (Torres-Santos et al., 1999). The antileishmanial activity observed was ascribed to a direct effect on the parasites, since the amount of nitric oxide produced by unstimulated and recombinant γ-interferon-stimulated macrophages was decreased rather than increased with DMC.

The lipophilic extract from *P. hispidum* had good *in vitro* antimalarial activity against *P. falciparum* sensitive to chloroquine, and resistant to chloroquine, with an IC_{50} of 7.6 and 13.0 µg/mL respectively (Jenett-Siems et al., 1999). Furthermore, the compound 2',4, 6'-trihydroxy-4'-methoxydihydrochalcone (**71**), isolated from this plant by bioactivity-guided fractionation, showed an antiplasmodial activity of 16.9 and 10.4 µg/mL for *P. falciparum* sensitive and resistant to chloroquine, respectively.

The ethanol extract from the fruits and leaves from *P. cumanense* displayed good *in vitro* activity against *Plasmodium falciparum* chloroquine resistant strain, with antimalarial activity below 1 µg/mL for both extracts (Garavito et al., 2006).

The antitrypanocidal activity of four natural chromenes, 2,2-dimethyl-2*H*-chromene-6-carboxylic acid (**72**), methyl-2,2-dimethyl-2*H*- chromene-6-carboxylate (**73**), compound **1** and methyl-2,2-dimethyl-8-(3'- methylbut-2'-enyl)-2*H*-chromene-6-carboxylate (**74**), isolated from the leaves of *P. aduncum* showed an IC_{50} of 558.3, 190.1, 44.8 and 33.2 µM, respectively, when evaluated by monitoring their effects on the growth of epimastigotes of *T. cruci* Y-strain (Batista et al., 2008). A comparative structure-activity analysis revealed the importance of both, a prenyl and an ester substituent in the chemical structure for achieving a strong antitrypanosomal activity.

Lopes et al. (2008) demonstrate a significant antitrypanosomal activity of the compound **29** isolated from the dried leaves of *P. crassinervium*. This prenylated hydroquinone showed an IC_{50} of 6.10 µg/mL, which was active in the same order of magnitude of the positive control benznidazole.

Flores et al. (2009) obtained two compounds with significant antiparasitic activity from the dichloromethane extract of leaves of *P. aduncum*. 3-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-benzoic acid (**75**) strongly inhibited the grow of *L. braziliensis*, with an IC_{50} 6.5 µg/mL, while 4-hydroxy-3-(3- methyl-1-oxo-2-butenyl)-5-(3-methyl-2-butenyl) benzoic acid (**76**) proved to be active against promastigotes of *L. amazonensis*, *L. braziliensis* and *L. donovani*, with an IC_{50} 17.8 µg/mL. This same compound exhibited moderate activity against epimastigote of *T. cruzi* with an IC_{50} 16.5 µg/mL. The bioactivity observed was related with shorter chains in the molecule, the presence of two isoprene moieties around the benzoic acid moiety (as for compound **76**), and the presence of $-OCH_3$ in the position C-4 of the aromatic ring for compound **75**.

Hexane fractions obtained from the leaves of *P. arboretum* and *P. tuberculatum* displayed strong activity against *T. cruzi*, the pathogenic agent of Chagas' disease which is a remarkable health problem in the undeveloped word (Regasini et al., 2009b). Both extracts showed an IC_{50} of 13.3 and 17.2 µg/mL respectively. Moreover, the hexane fractions from the fruits of *P. arboretum* and *P. tuberculatum* produced a significant inhibition on the epimastigote forms of the parasite with an IC_{50} of 31.3 and 32.2 µg/mL, respectively

In a multilateral effort to establish the medical potential of plants form Central and South America, Calderón et al. (2010), in a WHO funded project, assessed the antiparasitic activities of extracts obtained from several Piperaceae. The dichloromethane extract

obtained from the leaves of *P. aduncum* showed antiprotozoal activity (IC_{50}) of 38, 21 and higher than 50 µg/mL for *T. cruzi*, chloroquine-resistant *P. falciparum* and *L. mexicana*, respectively. The extract obtained from leaves of *P. dilatatum* exhibited activities of 31, 12 and higher than 50 µg/mL for the same species; whereas for *P. hispidum* the activities were 26, 22 and higher than 50 µg/mL for *T. cruzi*, chloroquine-resistant *P. falciparum* and *L. mexicana*, respectively. The ethanol extract obtained from leaves of *P. umbellatum* afforded an antiparasitic activity of 25 µg/mL on *T. cruzi*, and higher that 50 µg/mL for *P. falciparum* and *L. mexicana*, respectively.

The essential oil of the aerial part from *P. auritum* presented antileishmanial activity against the promastigotes of *L. major* (IC_{50} of 29.1 µg/mL), *L. mexicana* (IC_{50} of 63.3 µg/mL), *L. braziliensis* (IC_{50} of 52.1 µg/mL), and the most mortal causative agent of the disease, *L. donovani* (IC_{50} of 12.8 µg/mL) (Monzote et al., 2010).

The *in vivo* and *in vitro* antimalarial activities of compound **67** isolated from *P. peltatum* was evaluate by Rocha E Silva et al. (2011). The compound suppressed the growth of *P. berghei in vivo* when administrated orally and subcutaneously to mice at doses between 200-600 mg/kg/day by up to 63% after 4 days of treatments. A relevant chemosuppressive effect could be seen after five and seven days of oral administration at a concentration of 600 mg/kg/day (63.1% and 59.7% respectively). Moreover, the compound exhibited a significant *in vitro* antimalarial activity on standard and field *P. falciparum* strains, with an IC_{50} between 0.05 and 2.11 µg/mL depending on the strain.

Schistosomiasis is an important neglected disease, which is caused by the major agent in humans *Schistosoma mansoni* infecting over 200 million people worldwide, with 779 million people at risk of infection (Carrara et al., 2014). The dichloromethane fraction

obtained from the leaves of *P. amalago* (100 µg/mL) caused complete mortality on *S. mansoni*, and an important decrease in motor activity after 24 hours of incubation (Carrara et al., 2014). N-[7-(3´,4'-methylenedioxyphenyl)-2(*Z*),4(*Z*)-heptadienoyl] pyrrolidine (**77**) isolated from this fraction caused complete mortality of adult worms after 1 day incubation, at a concentration of 100 µM. Furthermore, this compound decreased the motor activity of male and female worms at concentration from 25 to 50 µM. These results validate the ethnobotanical use of this plant as vermifuge. This compound and N-[7-(3´,4'-methylenedioxyphenyl)-2(*E*),4(*E*)-heptadienoyl] pyrrolidine (**78**) isolated from the chloroform extract of the leaves of *P. amalago* were investigated for their activity against the promastigote form of *L. amazonensis* (Carrara et al., 2013). Both compounds inhibited the growth of the promastigote form of the parasite with an IC_{50} of 20 and 15 µM respectively.

The essential oils of *P. auritum*, *P. bredemeyeri*, *P. bogotense*, *P. marginatum* and *P. septuplinervium*, and their major compounds were evaluated against epimastigotes of *T. cruzi*, promastigotes of *L. infantum* and intracellular amastigotes of both species (Leal et al., 2013). The oils of *P. bogotense* (IC_{50} = 10.09 µg/mL), *P. marginatum* (IC_{50} = 16.15 µg/mL) and *P. septuplinervium* (IC_{50} = 13.98 µg/mL) reduced the growth of epimastigotes of *T. cruzi*. Only the essential oil of *P. septuplinervium* (IC_{50} = 30.05 µg/mL) inhibited the growth of the promastigote form of *L. infantum*. None of the oils was active against the extracellular amastigotes of both species. *α*-Pinene (**79**), found in the essential oils of *P. bredemeyeri*, *P. bogotense*, P. *marginatum* and *P. septuplinervium*, displayed activity against the epimastigote form of *T.cruzi* (IC_{50} = 2.74 µg/mL), the amastigote form of *T. cruzi* (IC_{50} = 1.92 µg/mL), and the promastigote form of *L. infantum* (IC_{50} = 45.94 µg/mL).

Limonene (**80**), presented in the essential oil of *P. bredemeyeri*, *P. bogotense*, and *P. marginatum* showed only activity on the epimastigote form of *T.cruzi* (IC_{50} = 38.71 µg/mL). Moreover, *trans-β*-caryophyllene (**81**), found in the essential oil of *P. bredemeyeri*, *P. bogotense*, *P. marginatum* and *P. septuplinervium*, showed activity against the epimastigote (IC_{50} = 2.89 µg/mL) and amastigote (IC_{50} = 24.54 µg/mL) forms of *T.cruzi*; and on the promastigote (IC_{50} = 24.02 µg/mL) and amastigote (IC_{50} = 53.39 µg/mL) forms of *L. infantum*.

The prenylated dihydrochalcone compound adunchalcone (**82**) obtained from the ethanol extract of the leaves of *P. aduncum* displayed inhibition on promatigote forms of *L. amazonensis*, *L. braziliensis*, and *L. chagasi*, with a EC_{50} of 11.03, 26.70 and 11.26 µM, respectively (Dal Picolo et al., 2014).

Recently, Araújo-Vilges et al. (2017) described the effect of **11**, isolated from the roots of *P. tuberculatum*, on *P. falciparum* and *L. amazonensis* studied *in vitro*. This compound inhibited the growth of both parasites, displaying more effectiveness against *P. falciparum* (IC_{50} = 3.2 µg/mL), after 72 hours of incubation, than for *L. amazonensis* (IC_{50} = 179.0 µg/mL). Although, the good activity showed by the compound for the promastigotes form of *L. amazonensis*, its specificity against the parasite was very low (SI = 1.3). On the other hand, **11** was more specific against *P. falciparum* than on *L. amazonensis* (SI = 72.5, after 72 hours of incubation). The authors suggested that for both parasites, the antiprotozoal activity of **11** might be due to the inhibition of the ubiquitin-proteasome system, which leads to the activation of apoptotic pathways and the decrease of cellular metabolism. Furthermore, for *P. falciparum*, **11** could be affecting the chances of parasites to

polymerize due to inhibition of the enzymatic activity related to the digestion of hemoglobin by the protozoa.

4.6. Diuretic Activity

Novaes et al. (2014) investigated the diuretic activity of the ethanol extract of dried leaves of *P. amalago*, which is used in the traditional Brazilian medicine for treatment of urinary tract disease. The diuretic activity assays were done on Wistar rats administrated orally with different doses of the extract (125, 250 and 500 mg/kg). The best results were obtained with a dose of 125 mg/kg after 24 h when compared with controls, with a diuretic index of 1.54. Moreover, the antilithiasic activity was determined *in vitro* measuring the calcium oxalate crystallization induced in human urine. The ethanol extract of *P. amalago* markedly reduced calcium oxalate crystallization at concentrations of 0.25, 0.5 and 1.0 mg/mL suggesting an antilithiasic activity.

4.7. Estrogenic and Serotonergic Activity

In an attempt to investigate the traditional use of *P. hispidum* by the *Q'eqchi* natives of Guatemala for treating women´s health diseases Michel et al. (2007) evaluated the estrogenic activity *in vitro* of the ethanol extract from the leaves of *P. hispidum* using ER_{α} and ER_{β} receptors. The extract revealed a strong activity in the ER_{β} receptor assay (76%) when tested at 100 µg/mL. Furthermore, the serotonergic activity of the extract was also evaluated *in vitro* through the $5\text{-HT}_{1A,5A,7}$ assay and revealed a strong activity at 50 µg/mL. The compound 9,10-methylenedioxy-5,6-*Z*-fadyenolide (**83**), isolated from the leaves, was identified to be responsible for the serotonergic activity observed, bounding to the 5-HT_{1A}

and 5-HT_7 receptors with a IC_{50} of 16.1 and 8.3μM respectively (Michel et al., 2010). Moreover, 5,6-*Z*-fadyenolide (**84**)and piperolide (**85**), also isolated from the plant, showed to be the estrogen agonists.

4.8. Inhibitory Effects on Phospholipases A_2

Núñez et al. (2005) investigated the inhibition of myotoxin I, which is a phospholipase A_2 from the snake *Bothrops asper*, by the methyl tert-butyl ether (MTBE) extracts from *P. peltatum* and *P. umbellatum*. Both extracts showed positive inhibitory activity against this enzyme. The fractionation of both extracts yielded the compound **67**, which inhibited completely the activity of myotoxin I, with an inhibitor-toxin ratio of 10:1, and IC_{50} of approximately 1.0 mM. Moreover, representatives groups of phospholipases I and III were also inhibited by this compound. Major changes in hydrophobicity, gross molecular mass and in protein charge could explain in part the inhibition mechanism.

4.6. Insecticidal Activity

The bioactivity of different Piperaceae species of Panama have been studied against the mosquito *Aedes aegypti*, which is an important vector of dengue, Zika, and Chikungunya viruses.

Dillapiole (**65**), a compound obtained from the essential oils of young dried leaves of *P. aduncum*, was tested on pupae and larvae of *A. aegypti* (Rafael et al., 2008) . The data revealed that **65** reduces reproduction and survival of the mosquito. On the other hand, it induces micronuclei and chromosomal damage, which pointed out that these genotoxic effects might lead to its use as an alternative for the control of *A. aegypti*.

Santana et al. (2015) evaluated the larvicidal activity of the essential oils obtained from the leaves of *P. aduncum*, *P. marginatum* and *P. arboreum* against *A. aegypti*. *P. marginatum* showed the lowest lethal concentration (LC_{50}, 34 ppm), calculated from mortality data from 24 to 48 hours; while the essential oil of *P. aduncum* and *P. arboreum*, revealed a LC_{50} of 46 and 55 ppm, respectively. The authors suggested that anethol (**86**) could be the main compound that accounts for the observed larvicidal activity. Previously, Autran et al. (2009) evaluated the bioactivity of the oil from different parts of *P. marginatum* (leaf, stem, inflorescense), identifying in the inflorescense the most potent larvicidal activity (LC_{50}, 19.9 ppm). On the other hand, the essential oil of the leaves had a higher activity (LC_{50}, 23.8 ppm) than that reported by Santana et al. (2015) (LC_{50}, 34.0 ppm), which could be to the different chemotypes of the plant. The oil obtained from Autran et al. (2009) has the main compound *Z*-asarone (**87**) as the major compound. Moreover, the larvicidal activity of *P. arboreum* reported in the study by Santana et al. (2015) could be due to the presence of germacrene D (**88**), which has showed mosquitocidal activity against other mosquitoes of the genera *Culex*, *Aedes*, and *Anopheles*.

The larvicidal activity against *A. aegypti* of the essential oils obtained from the leaves of 11 Panamanian *Piper* species was investigated by Santana et al. (2016). The essential oils of *P. longispicum* and *P. hispidum* exhibited activity at a concentration of 250 µg/mL.

4.7. Local Anesthetic Activity

Pipercallosine (**89**), which was isolated from *Piper darienense* by Rodriguez et al. (2005), showed local; anesthetic activity. The evaluation of local anesthetic activity was carried out by the Guinea pig wheal method, using 2% of lidocaine as standard vs 2% pipercallosine.

Both compounds showed 100% of local anesthetic activity after 1 min of treatment. After 120 min, **89** showed 13.8% of local anesthetic activity, where as lidocaine showed only 10% of activity.

5. Toxicity

The chromene derivative **1**, isolated from the petrol extract of the leaves of *P. aduncum* showed molluscicidal activity on the *B. glabrata* test (MIC of 30 ppm) (Orjala et al., 1993). Gupta et al. (1996) evaluated the cytotoxicity of the methanol extract of the aerial parts of *P. auritum in vitro* by a clonogenic assay after treatment with the extracts of V79 (Chinese hamster lung fibroblasts cells) suspension cultures. The extract showed cytotoxicity (survival factor below 10%) at aerobic and hypoxic conditions. Furthermore, the toxicity of tinctures obtained from the foliage of this plant was evaluated *in vitro*, using *A. salina* bioassay, and *in vivo* for establishing acute toxicity by using Swiss albino mice. The extract showed a dose dependent mortality, with a LC_{50} in the *A. salina* test of 26.67 µg/mL, and 1082 mg/kg in the *in vivo* studies (Lagarto et al., 2001).

Assis et al. (2013) studied the cytotoxicity of the essential oil extracted from fresh leaves of *P. hispidum*. The oil displayed lethality against *A. salina*, with a LC_{50} of 404.80 µg/mL. In one study, the toxicity of the ethanol extract from the leaves of *P. hispidum* was evaluated by the Alamar Blue assay and *in vivo* on Swiss-Webster mice (da Silva et al., 2014). The extract was nontoxic *in vitro* (IC_{50} > 200 µg/mL). Moreover, when the extract was administered to the mice at doses higher than 2000 mg/kg, no symptoms of toxicity was observed.

Morphometric analysis and osmotic fragility tests have been used in order to evaluate the cytotoxic effects and the interaction of essential oils by using membranes of red blood cells (Barros et al., 2016). This methodology was used to assess the toxicity of the essential oil from the leave of *P. aduncum* (Barros et al., 2016). The oil increased significantly the hemolysis and leads to modifications to the morphology or the red blood cells. The latter caused an increment on the permeability and diffusion of the oil, causing toxicity on the cells membranes.

Bru et al. (2016) have reviewed the toxicity of the essential oils, extracts and compounds obtained from different parts of *P.marginatum*. The water extract, the ethanolic extracts and the essential oils of the plant have displayed toxicity *in vitro* (on Vero and carcinoma cells) and *in vivo* (on Winstar adult rats) at different concentrations.

Overall, although there is an important amount of data on the biological activities of *Piper* species there are limited data on their toxicological activity, an aspect that need to be further evaluated in future investigations.

6. Clinical trials

To our knowledge there are no reports on clinical trials of Panamanian species of *Piper* nor their constituents.

7. Concluding remarks

Investigations on the use of *Piper* species prevalent in Panama for the treatment of diseases is based mainly on the ethnopharmacological knowledge, and *in vitro* studies. The pharmacological studies are still limited, in spite of the promising results reported to date.

The pharmacological research indicated that these plants are active as antibacterial, antifungal, anti-inflammatory, anti-cancer, antidiabetic, antiulcer, antiprotozoal, estrogenic, diuretic, anti-snake venom , local anesthetic and as insecticidal. In Panama the most significant ethnomedical uses that stand out for Panamanian species of *Piper* are: skin infections, to alleviate colds and treat snakebites, toothache, fish poison, muscle aches, female disorders, wound healing and insecticidal activities. In some cases the ethnomedical use may have some justification, for example, antifungal activity for skin infections, local anesthetic activity of pipercallosine in *Piper darienense*. A careful analysis of ethnomedical uses of Panamanian Piper species indicated that there was no similarity among Panamanian uses versus their uses in other countries. Thus, this review provides a good lead for future chemical and biological investigations on unexplored Piper species.

Altogether, these results point out the great potential of these plants for obtaining active compounds that might be used to alleviate or prevent diseases. Nevertheless, the assessment of extracts *in vivo* and compounds isolated from the plants that allows for a deeper comprehension of their bioactivity is an important challenge that needs to be addressed. Moreover, more studies are needed in order to have more insights on the toxicology of the extracts and natural products from these *Piper* species. Unfortunately, there are no clinical trials reported to date by using any compound obtained from the *Piper* species occurring in Panama. Therefore the systematic use of these Piperaceae as therapeutic agents in modern medicine seems to still be a challenge.

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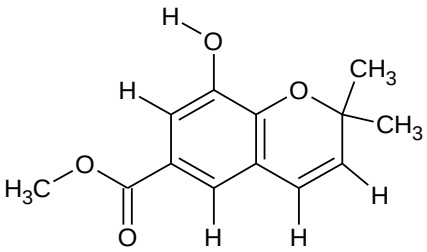

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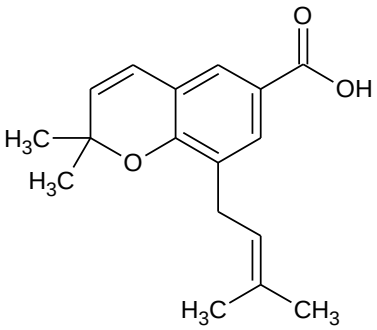

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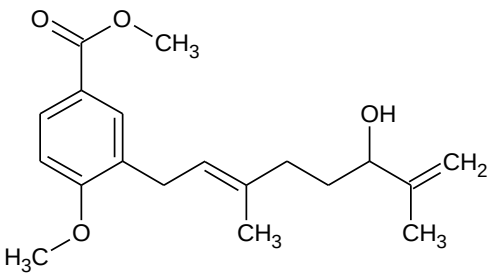

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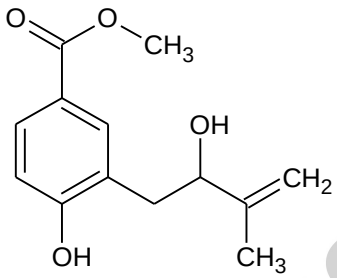

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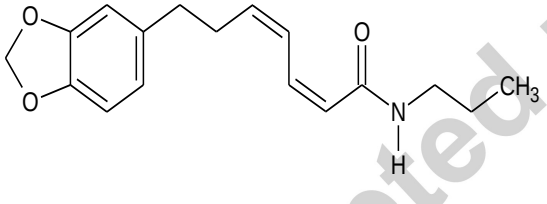

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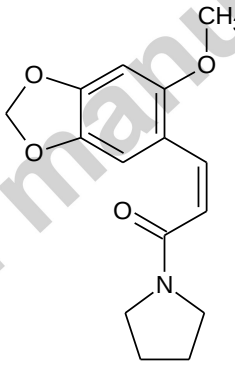

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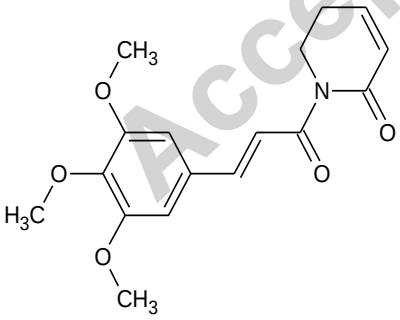

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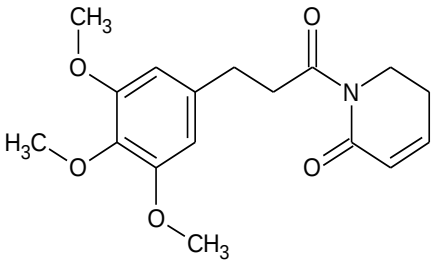

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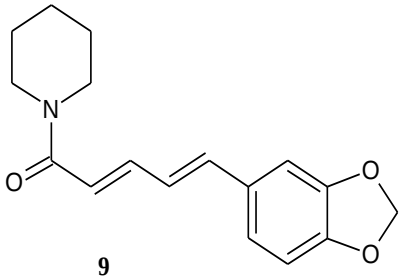

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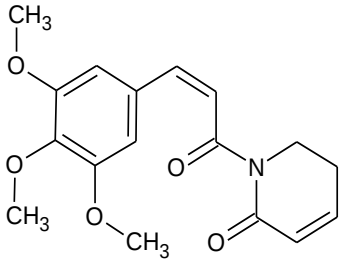

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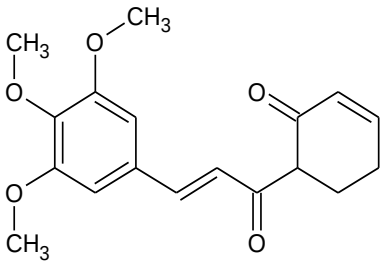

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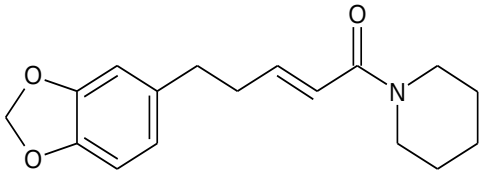

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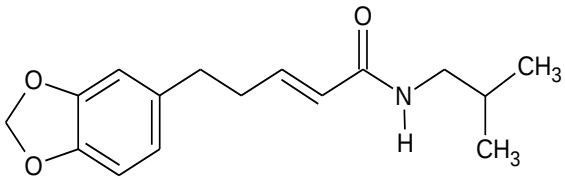

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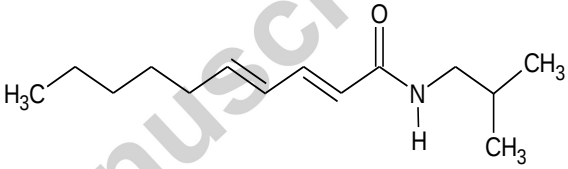

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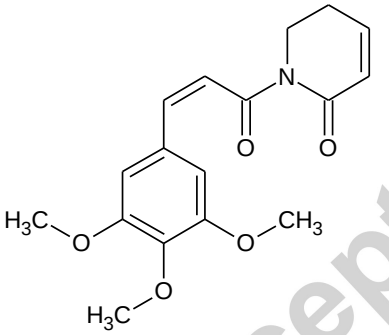

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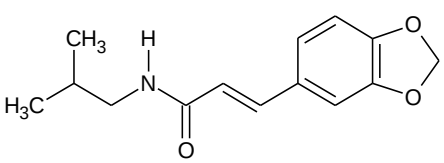

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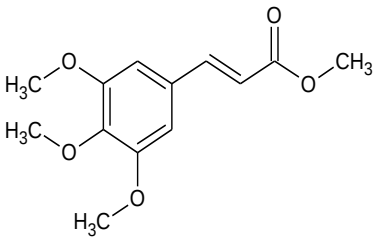

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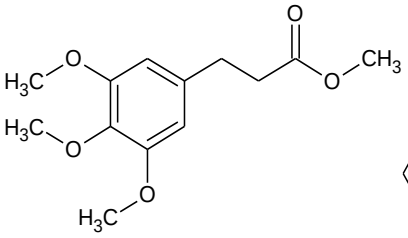

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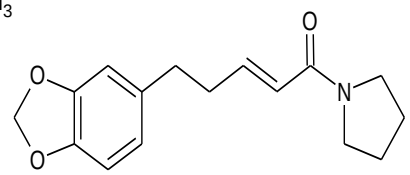

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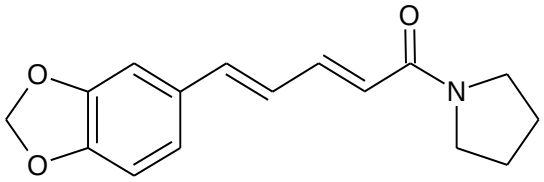

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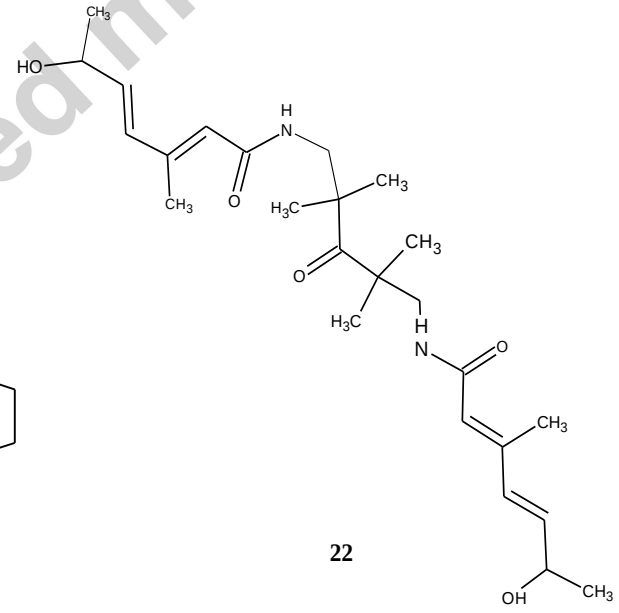

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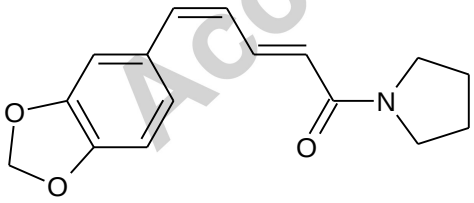

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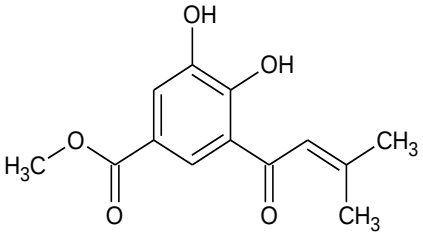

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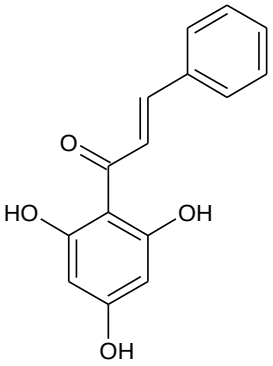

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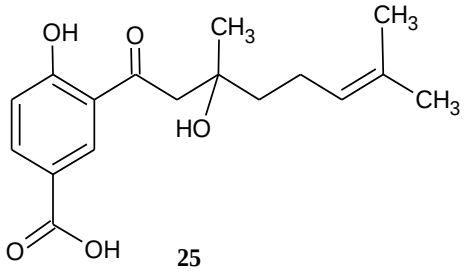

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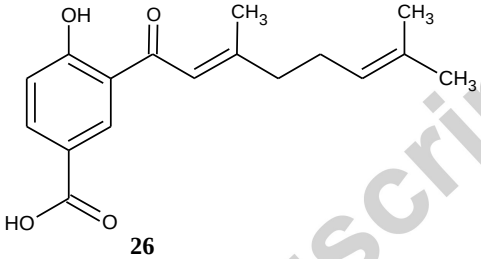

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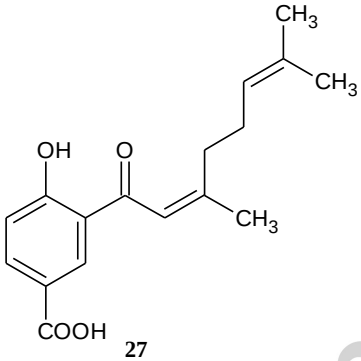

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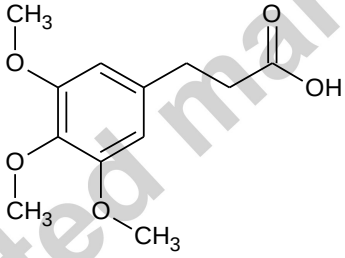

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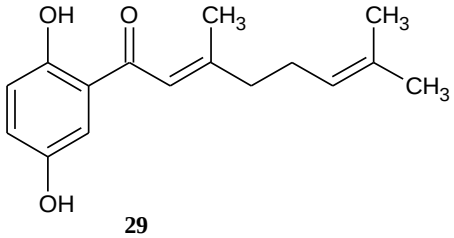

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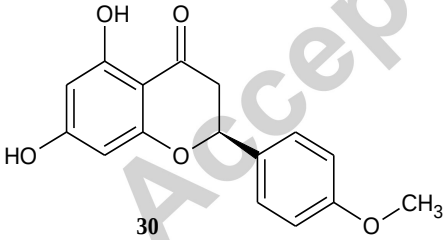

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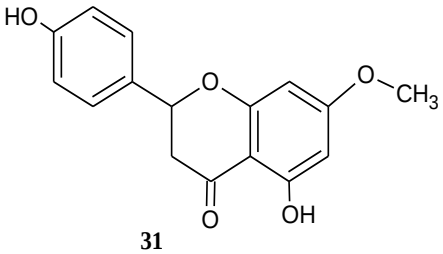

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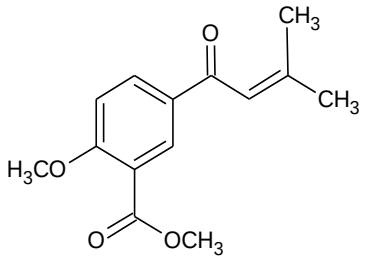

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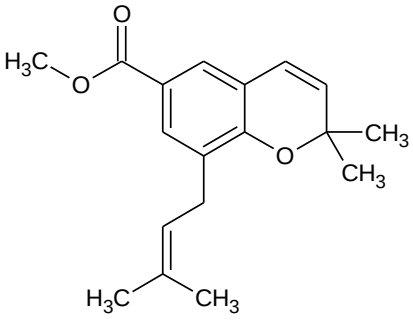

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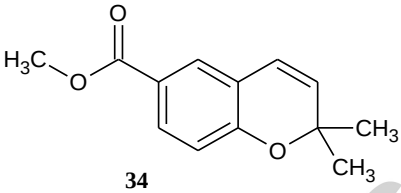

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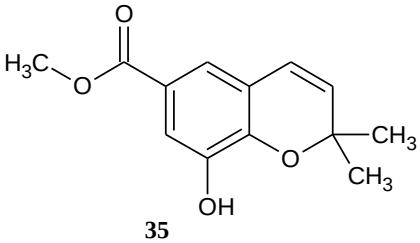

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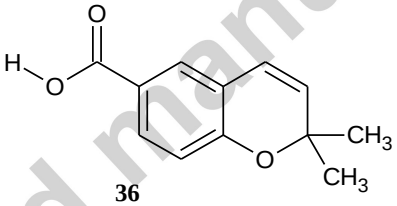

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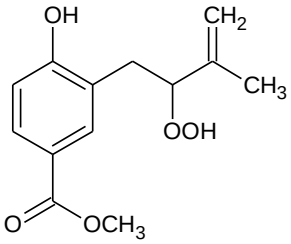

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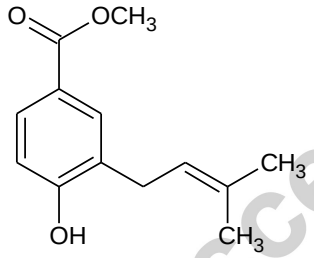

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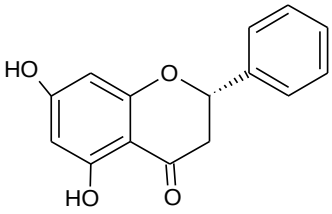

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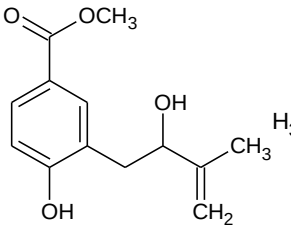

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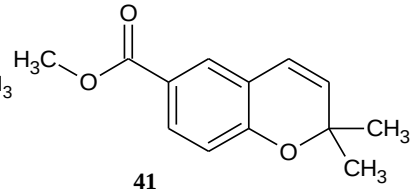

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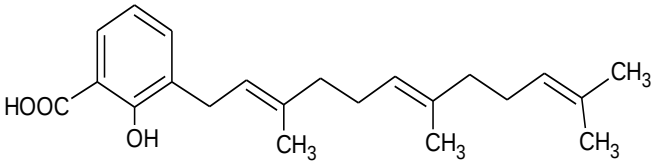

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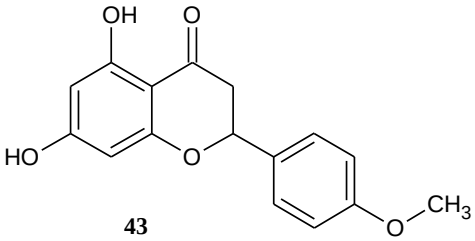

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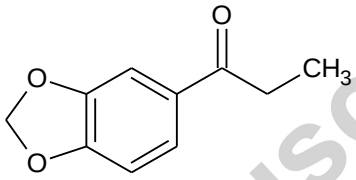

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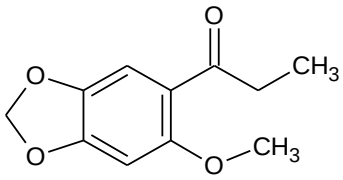

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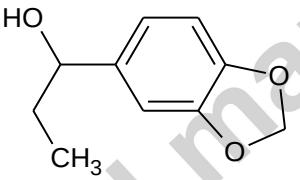

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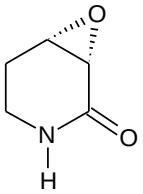

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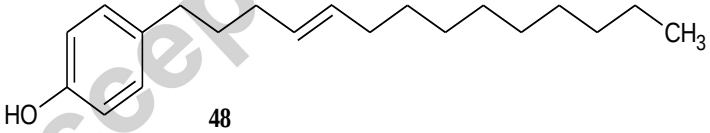

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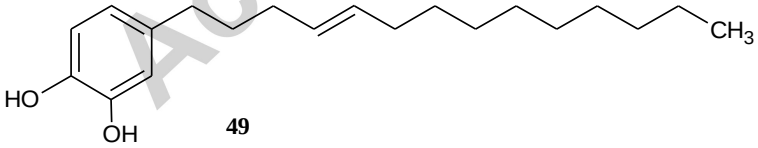

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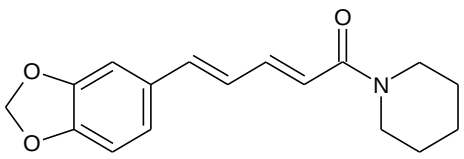

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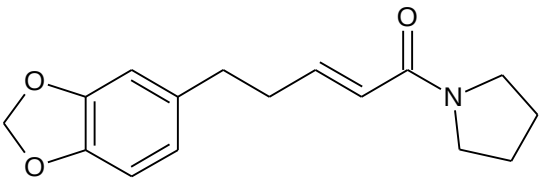

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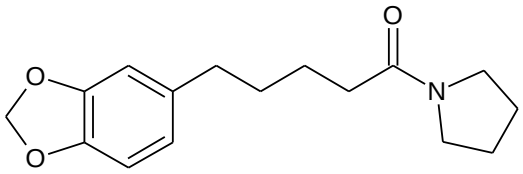

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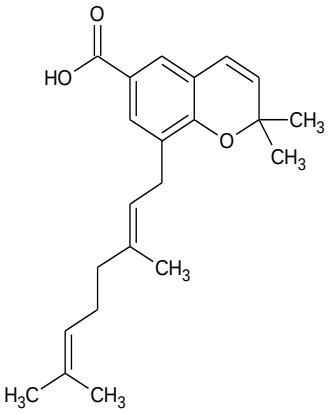

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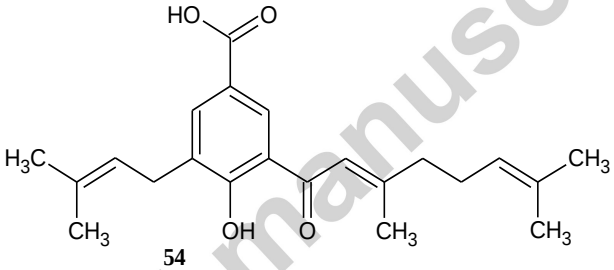

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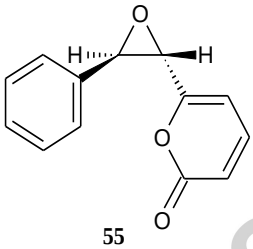

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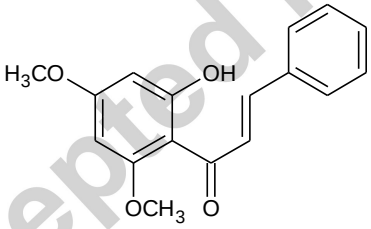

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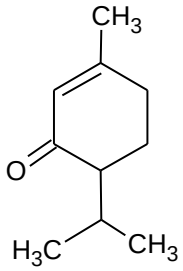

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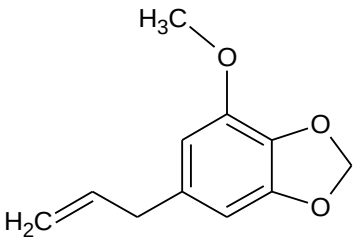

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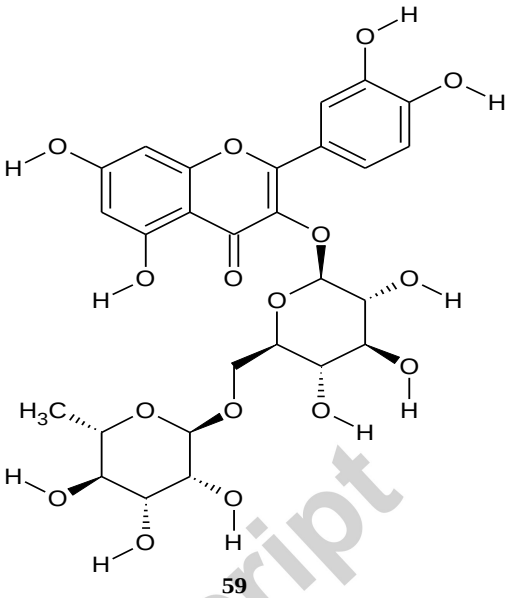

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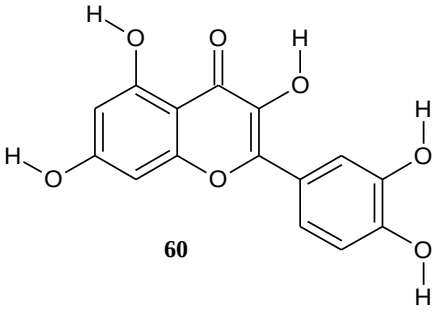

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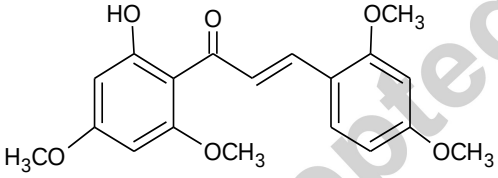

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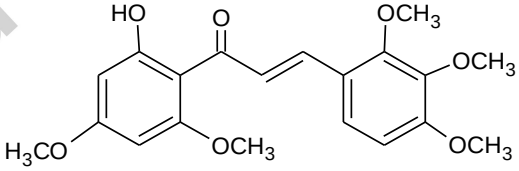

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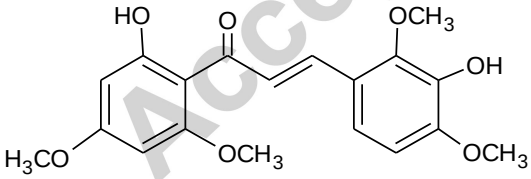

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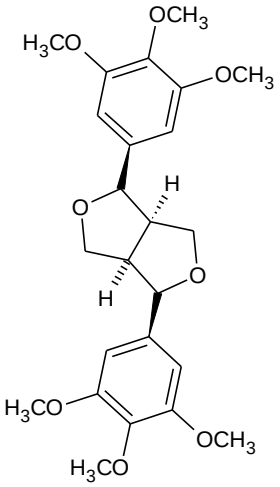

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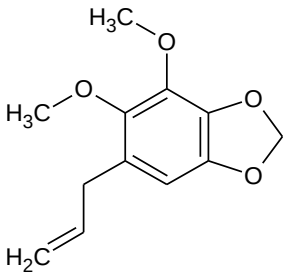

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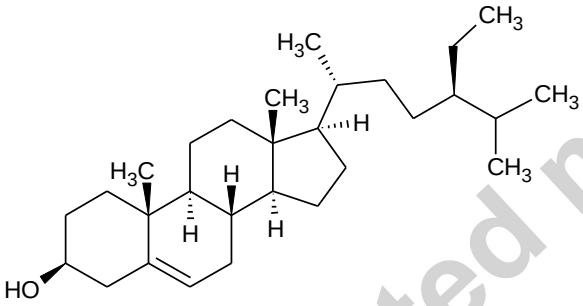

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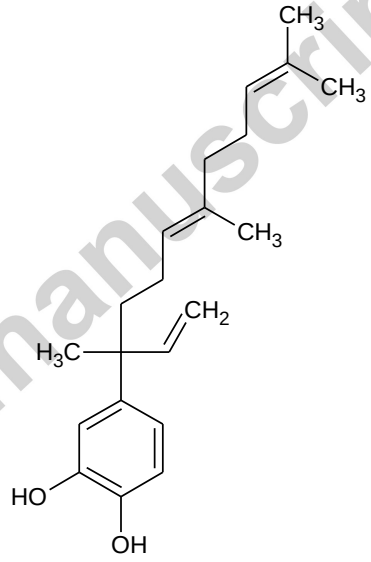

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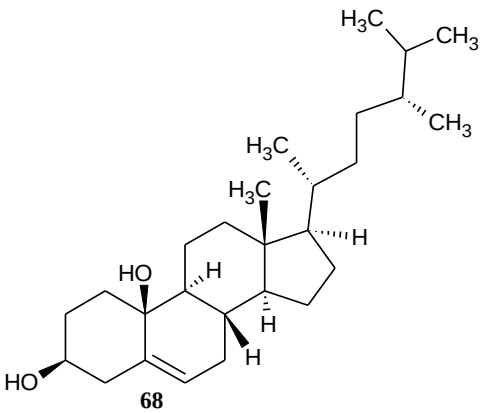

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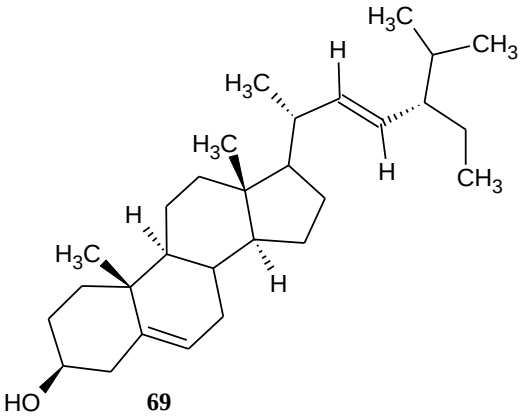

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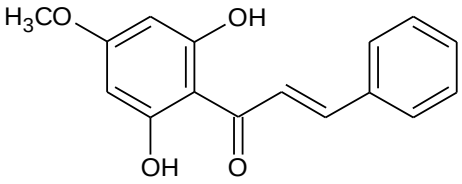

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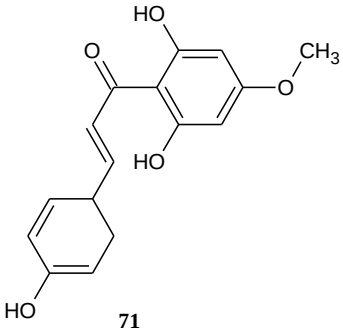

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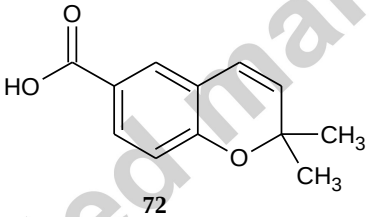

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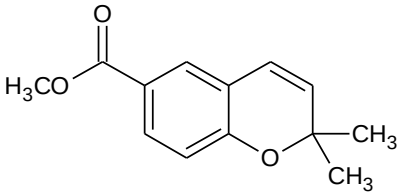

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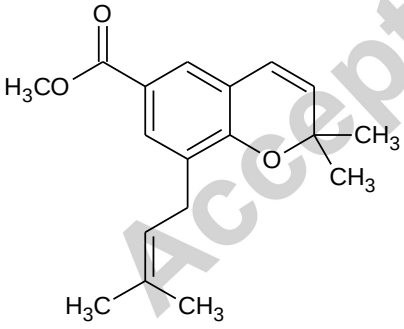

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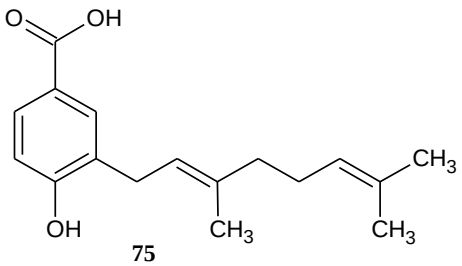

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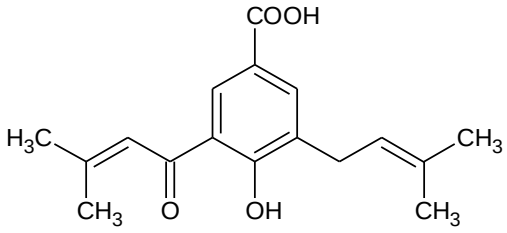

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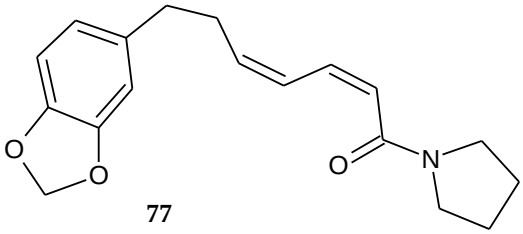

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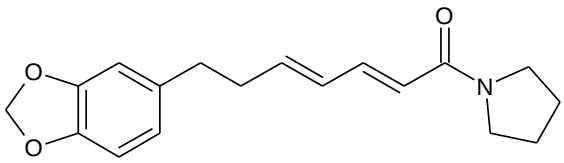

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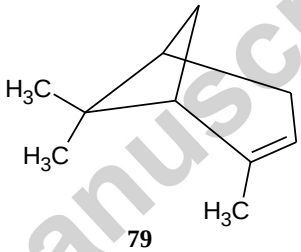

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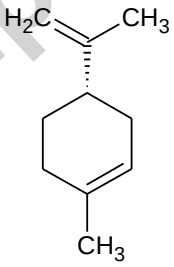

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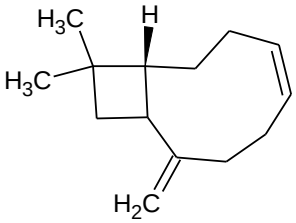

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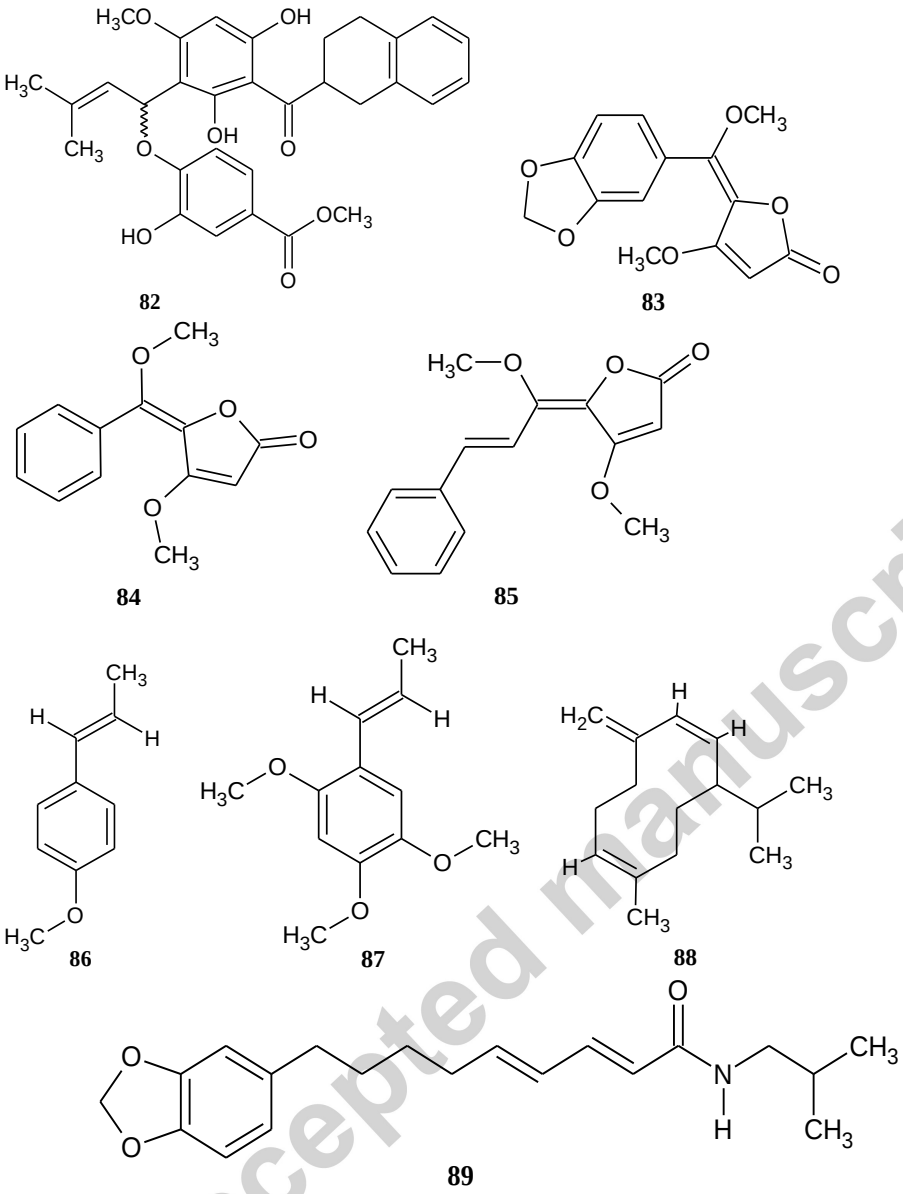

Fig. 1. Chemical structures of active compounds identified in Panamanian *Piper* species.

Table 1 Ethnomedical uses of species of *Piper* occurring in Panama

Scientific name	Part used	Traditional uses	Country	References
P. aduncum L.	Aerial parts	Treating rheumatic afflictions, and as an astringent, styptic and antiseptic	Peru	Kloucek et al. (2005)
	Bark	Treatment of toothache, diarrhea, dysentery, scabies, cuts, cough and fungal infections	Papua New Guinea	Siges et al. (2005)
	Leaves	Treatment of intestinal and stomach ailments	Brazil	Vandenberg (1993)
	Leaves	Treat insect bites, dressing for sores and cuts, and scabies	Papua New Guinea	Siges et al. (2005)
	Leaves	General infections and fever	Peruvian Amazon	Valadeau et al. (2009)
	Leaves	Treating erysipelas, cystitis, gynecological inflammation, disorders of the digestive tract, wound healing and pyelitis	Brazil	Vieira (1991); Vandenberg (1993); Coimbra (1994); De Almeida et al. (2009)
	Leaves and fruits	Antimycotic, antimicrobial and styptic	Amazon region	Schultes and Raffauf (1990)
	Leaves, fruits and stems	Treatment of female disorders, pains, as digestive and skin cleanser	Honduras	Lentz et al. (1998)
	NS	Treat diseases of the digestive tract, flu and as insect repellent	Brazil	Potzernheim et al. (2012)
	NS	Treat dysentery and hemostasis	Colombia	Diaz et al. (1984)
	NS	Treat burns	Indonesia	Lohézic-Le Dévéhat et al. (2002)
	NS	Stomach aches and cold	Jamaica	Burke and Nair (1986)

	NS	Treatment of diarrhea	Peru	Macedo and Oviedo (1987)
	Roots	Treat stomach and respiratory ailments, wounds and dysentery	Papua New Guinea	Siges et al. (2005)
	Stem and fruits	Treating headache and toothache	Papua New Guinea	Siges et al. (2005)
Piper amalago L.	Bark	Treat cough, gastrointestinal and chest pains	Mexico	Domínguez and Alcorn (1985); Dominguez et al. (1986)
	Leaves	Treatment of burns	Brazil	Alves et al. (2008); Novaes et al. (2014)
	Leaves	Treatment of headache, nosebleed, pains, sores, and to prevent miscarriage	Mexico	Domínguez and Alcorn, (1985); (Dominguez et al. (1986)
	NS	Diuretic, for treating hypertension and renal calculi	Brazil	Alves et al. (2008); Novaes et al. (2014).
	NS	To treat edema, inflamations and as an antipyretic	Mexico	Domínguez and Alcorn (1985); Dominguez et al. (1986)
	Tender shoots	To treat vertigo problems	Mexico	Domínguez and Alcorn (1985); Dominguez et al. (1986)
Piper arboreum Aubl .	Inflorescense	Treatment of liver pains	Panama	Gupta et al. (1993)
	Leaves	Treatment of liver pains	Panama	Gupta et al. (1993)
	NS	Treat sexually transmitted diseases, bronchitis, urinary infections, rheumatic problems and as carminative	Brazil	Bezerra et al. (2007); De S. Luna et al. (2005); Regasini et al. (2009); Tintino et al. (2014).
	NS	As sedative and to counteract the effects of snakes bites	Brazil	Bezerra et al. (2007); De S. Luna et al.

				(2005); Regasini et al. (2009); Tintino et al. (2014)
Piper auritum Kunth	Inflorescence	Treating common colds	Panama	Gupta et al. (1993)
	Leaves	Treating against snakebites	Colombia	Vásquez et al. (2013)
	Leaves	Treat headaches	Costa Rica	Tucker and Maciarello (1998)
	Leaves	Applied to remove ticks	El Salvador	Schultes (1975)
	Leaves	Facilitate childbirth and as emmenagogue	Mexico	Browner (1985)
	NS	Treatment of dysmenorrhea and as galactagogue	Guatemala	Michel et al. (2007)
	NS	Wound healing	Mexico	Caamal-Fuentes et al. (2011)
Piper cordulatum C.DC.	NS	Remedy for skin infections	Panama	Roming et al. (1992)
Piper darienense C.DC.	Leaves	As bath to alleviate colds and to treat snakebites; toothache and fish poison	Panama	Rodríguez et al (2005)
Piper hispidum Sw.	Inflorescence	Applied topically for muscle aches	Panama	Gupta et al. (1993)
	Leaves	Treating anti-hemorrhagic and diuretic	Brazil	da Silva et al. (2014)
	Leaves	Treating malaria	Colombia	Friedrich et al. (2005)
	Leaves	Treating conjunctivitis, diarrhea and hemorrhages	Panama	Gupta et al. (1993)
	Leaves	Prevention of tooth decay	Peru	Lewis and Elvin-Lewis (1984)
	Leaves	Treatment of female diseases	Guatemala	Michel et al. (2007)
	Leaves	Remedy to ease the pain of childbirth,	Nicaragua	Michel et al. (2007)

		anemia, and rheumatism		
	Leaves	Treatment of mumps and tonsillitis	Mexico	Martinez (1984)
	Leaves	Treating leishmaniasis and for cicatrization of wounds	Peru	Estevez et al. (2007)
	NS	Applied on head to kill lice	Ecuador	Schultes (1975)
	NS	Treatment of snake and insect bites, and as skin cleanser	Honduras	Lentz et al. (1998)
	NS	Treat stomach aches and colds	Jamaica	Burke and Nair (1986)
Piper marginatum Jacq.	Leaves	Treatment of malaria	French Guyana	Vigneron et al. (2005)
	NS	Antidote for snakebites, as antispasmodic, carminative, antispasmodic, diuretic, for blood pressure control, for treatment of asthma, erysipela, problems of the urinary system, gall bladder and liver diseases	Brazil	De Oliveira Chaves and De Oliveira Santos (2002); de Albuquerque et al. (2007); Reigada et al. (2007)
	NS	Treat female disorders and to help during parturition	Trinidad and Tobago, Puerto Rico and Surinam	Bru and Guzman (2016)
Piper multiplinervium C.DC.	Leaves	Treating different types of pains	Panama	Gupta et al. (1993)
Piper obliquum Ruiz & Pav.	Leaves	Treating pains, muscular aches and for arthritis	French Guyana	DeFilipps et al. (2004)
	NS	Treat dental problems	Ecuador	DeFilipps et al. (2004)
	Stem	Remedy for hernia	French Guyana	DeFilipps et al. (2004)
Piper peltatum	Leaves and	Treatment of	Brazil	Pinto et al.

L.	roots	erysipela, malaria, leishmaniasis and hepatitis		(2010)
Piper umbellatum L.	NS	Treatment of the urinary tract infections, skin and liver ailments, contusions, digestive problems, pains, wound healing, swelling, rheumatism, women's diseases, as antipyretic and anti-inflammatory	Africa, Asia and Latin America	Roersch, (2010)

NS: Not specified

Table 2 Pharmacological activities of compounds and extracts of the genus *Piper* from Panama

Pharmacological activity	Plant species	Compound/Extract	Activity	References
Antimicrobial activity	*P. aduncum*	Methyl-8-hydroxy-2,2-dimethyl-2*H*-chromene-6-carboxylate	Antibacterial activity against *B. subtilis* (MIC of 8.5 nmol), *E. coli* (MIC of 8.5 nmol), and *M. luteus* (MIC of 8.5 nmol); Antifungal activity against *P. oxalicum* (MIC of 17 nmol)	Orjala et al. (1993)
		2,2-dimethyl-8-(3-methyl-2-butenyl)-2*H*-chromene-6-carboxylic acid	Antibacterial activity against *B. subtilis* (MIC of 2.0 nmol) and *M. luteus* (MIC of 3.2 nmol); Antifungal activity against *P. oxalicum* (MIC of 15.5 nmol)	Orjala et al. (1993)
		Methyl-3-(6- hydroxy-3,7-dimethyl-2,7-octadienyl)-4-methoxy-benzoate	Antibacterial activity against *M. luteus* (MIC of 10.8 nmol), and *B. subtilis* (MIC of 10.8 nmol)	Orjala et al. (1993)
		Methyl-3-(2-hydroxy-3-methyl-3-butenyl)-4-hydroxybenzoate	Antibacterial activity against *M. luteus* (MIC of 6.6 nmol) and *B. subtilis* (MIC of 13.0 nmol)	Orjala et al. (1993)
		Aduncumene	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg). and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2004)
		Methyl-2,2-dimethyl-8-(3'-methyl-2'-butenyl)-2*H*-1-benzopyran-6-carboxylate	Antifungal activity against *C. cladosporioides* (MAR of 0.1 µg) and *C. sphaerospermum* (MIC of 0.1 µg)	Lago et al. (2004)

Methyl-2,2-dimethyl-2*H*-1-benzopyran-6-carboxylate	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg), and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2004)
Methyl-8-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carboxylate	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg)and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2004)
2,2-dimethyl-2*H*-1-benzopyran-6-carboxylic acid	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg) and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2004)
Essential oil (fruits)	Antifungal activity against *Cladosporium cladosporioides* (MIC of 10 µg)	Navickiene et al. (2006)
Methanol extract (leaves)	Antifungal activity against *C. albicans* (MIC of 1.25 mg/mL)	Braga et al. (2007)
Methyl-4-hydroxy-3-(2'-hydroperoxy-3'-methyl-3'-butenyl) benzoate	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Lago et al. (2009)
Methyl-4-hydroxy-3-(3'-methyl-2'-butenyl) benzoate	Antifungal activity against *C. cladosporioides*, and *C. sphaerospermum* (MAR of 1 µg)	Lago et al. (2009)
Pinocembrin	Antifungal activity against *C. cladosporioides*	Lago et al. (2009)

		(MAR of 1 µg), and *C. sphaerospermum* (MAR of 1 µg)	
	Methyl-4-hydroxy-3-(2'-hydroxy-3'-methyl-3'-butenyl) benzoate	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Lago et al. (2009)
	Methyl-2,2-dimethyl-2*H*- 1-benzopyran-6-carboxylate	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg), and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2009)
	Methyl-2,2-dimethyl-8-hydroxy-2*H*-1-benzopyran-6-carboxylate	Antifungal activity against *C. cladosporioides* (MAR of 5.0 µg), and *C. sphaerospermum* (MAR of 5.0 µg)	Lago et al. (2009)
	Essential oil (aerial parts)	Antifungal activity inhibition of *T. mentagrophytes* and *T. tonsurans* (MIC of 500 µg/mL)	Guerrini et al. (2009)
	Essential oil (leaves)	Antifungal activity against *Cryptococcus neoformans* (MIC of 62.5 µg/mL)	Morandim-Giannetti et al. (2010)
	Essential oil (aerial parts)	Antibacterial activity against *S. aureus* (MIC of 500 µg/mL) and *S. epidermidis* (MIC of 250 µg/mL)	Brazao et al. (2014)
P. arboreum	N-[10- (13,14-methylenedioxyphenyl)-7(*E*)-pentaenoyl]-pyrrolidine	Antifungal activity against *C. sphaerospermum* (MAR of 0.1 µg)	Vasques et al. (2002)
	N-[10-(13,14-	Antifungal activity	Vasques et

		methylenedioxyphenyl)-7(*E*), 9(*E*)-pentadienoyl]-pyrrolidine	against *C. sphaerospermum* (MAR of 0.1 μg)	al. (2002)
		N-[10-(13,14-methylenedioxyphenyl)-7(*E*), 9(*Z*)-pentadienoyl]-pyrrolidine	Antifungal activity against *C. sphaerospermum* (MAR of 10 μg)	Vasques et al. (2002)
		Arboreumine	Antifungal activity against *C. sphaerospermum* (MAR of 5 μg)	Vasques et al. (2002)
		Piperyline	Antifungal activity against *C. krusei* and *C. parapsilosis* (MIC between 15.6 and 31.2 μg/mL)	Regasini et al. (2009)
		4,5-dihydropiperyline	Antifungal activity against *C. krusei* and *C. parapsilosis* (MIC between 15.6 and 31.2 μg/mL); *C. neoformans* (MIC of 31.2 μg/mL)	Regasini et al. (2009)
		Tetrahydropiperyline	Antifungal activity against *C. krusei* and *C. parapsilosis* (MIC between 15.6 and 31.2 μg/mL); *C. neoformans* (MIC of 15.6 μg/mL)	Regasini et al. (2009)
	P. bogotense C.DC.	Essential oils (stems and leaves)	Antifungal activity against *Trichophyton rubrum* (MIC of 79 μg/mL) and *T. mentagrophytes* MIC of 15.6 μg/mL)	Tangarife-Castaño et al. (2014)
	P. bremedeyeri J. Jacq.	Essential oils (stems and leaves)	Antifungal activity against *Trichophyton rubrum* (MIC of 157 μg/mL) and *T. mentagrophytes* (MIC of 125 μg/mL)	Tangarife-Castaño et al. (2014)

P. crassinervium Kunth	Crassinervic acid	Antifungal activity against *C. cladosporioides* (MAR of 0.5 µg), and *C. sphaerospermum* (MAR of 0.5 µg)	Lago et al. (2004)
	4-hydroxy-(3',7'-dimethyl-1'- oxo-octa-2'-*E*-6'-dienyl) benzoic acid	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Lago et al. (2004)
	4-hydroxy-(3',7'-dimethyl-1'-oxo-octa-2'-*Z*-6'-dienyl) benzoic acid	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Lago et al. (2004)
	3,4,5-trimethoxydihydro-cinnamic acid	Antifungal activity against *C. cladosporioides* (MAR of 10.0 µg) and *C. sphaerospermum* (MAR of 10.0 µg)	Lago et al. (2004)
	1,4-dihydroxy- 2-(3',7'-dimethyl-1'-oxo-2'-*E*-6'-octadienyl) benzene	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Danelutte et al. (2003);
	Naringenin 4'-methylether	Antifungal activity against *C. cladosporioides* (MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	Lago et al. (2004)
	Sakuranetin	Antifungal activity against *C. cladosporioides*	Lago et al. (2004)

			(MAR of 1.0 µg), and *C. sphaerospermum* (MAR of 1.0 µg)	
		3α,4α-epoxy-2-piperidone	Antifungal activity against *C. cladosporoides* (MIC= 1 µg) and *C. sphaerospermum* (MIC= 1 µg)	Lago and Kato (2007)
		Essential oil (leaves)	Antifungal activity against *Candida albicans*, *C. krusei*, *C. neoformans* and *C. parapsilosis* (MIC > 250 µg/mL)	Morandim-Giannetti et al. (2010)
	P. cumanense Kunth	Cumanensic acid	Antifungal activity against *Botrytis cinerea* (MIC of 100 µg) and *Fusarium oxysporum* (MIC of 1 µg)	Parra et al. (2011)
	P. dilatatum Rich.	(+)-(7S,8R)-epoxy-5,6-didehydrokavain	Antifungal activity on *C. cladosporioides* (MIC 1 of µg) and *C. sphaerospermum* (MIC 1 of µg)	dos Santos et al. (2013)
		Flavokavain B	Antifungal activity on *C. cladosporioides* (MIC of 100 µg) and *C. sphaerospermum* (MIC of 100 µg)	dos Santos et al. (2013)
	P. hispidum	Essential oil (leaves)	Antifungal activity against *cladosporioides* and *C. sphaerospermum*, with a detection limit of 0.1 µg and 1.0 µg respectively	Da Silva et al. (2014)
		Essential oils (stems and leaves)	Antifungal activity against *Trichophyton*	Tangarife-Castaño et

			rubrum and *T. mentagrophytes* (MIC of 125 µg/mL) and *T. rubrum* (MIC of 99 µg/mL)	al. (2014)
		Hydroalcoholic extract (leaves)	Antibacterial activity against *S. aureus* (MIC of 62.5 µg/mL) and Antifungal activity against *C. albicans* (MIC of 62.5 µg/mL)	Costa et al. (2016)
		2'-hydroxy-4,4',6'-trimethoxychalcone	Antibacterial activity against *S. aureus* (MIC of 125 µg/mL) and Antifungal activity against *C. albicans* (MIC of 250 µg/mL)	Costa et al. (2016)
		2'-hydroxy-3,4,4',6'-tetramethoxychalcone	Antibacterial activity against *S. aureus* (MIC of 250 µg/mL)	Costa et al. (2016)
		3,2'-dihydroxy-4,4',6'-trimethoxychalcone	Antibacterial activity against *S. aureus* (MIC of 125 µg/mL) and antifungal activity against *C. albicans* (MIC of 500 µg/mL)	Costa et al. (2016)
	P. lanceaefolium Kunth	Lanceafolic acid methyl ester	Antifungal activity against *C. albicans* (MIC of 100 µg/mL)	López et al. (2002)
		Pinocembrin chalcone	Antifungal activity against *C. albicans* (MIC of 100 µg/mL)	López et al. (2002)
	P. marginatum	5,4'-dihydroxy-7-methoxyflavanone	Antifungal activity against *C. cladosporioides* (MIC = 1.0 µg) and *C. sphaerospermum*	Reigada et al. (2007)

			(MIC = 1.0 µg)	
		5,7-dihydroxy-4'-methoxyflavanone	Antifungal activity against *C. cladosporioides* (MIC = 1.0 µg) and *C. sphaerospermum* (MIC = 1.0 µg)	Reigada et al. (2007)
		3,4-methylenedioxypropio-phenone	Antifungal activity against *C. cladosporioides* and *C. sphaerospermum* (MIC of 5.0 µg for both strains)	Reigada et al. (2007)
		2-methoxy-4,5-methylenedioxypropio-phenone	Antifungal activity against *C. cladosporioides* (MIC of 5.0 µg) and *C. sphaerospermum* (MIC of 5.0 µg)	Reigada et al. (2007)
		1-(3,4-methylenedioxyphenyl) propan-1-ol	Antifungal activity against *C. cladosporioides* and *C. sphaerospermum* (MIC of 10 µg for both strains)	Reigada et al. (2007)
		Essential oil (stems and leaves)	Antifungal activity against *Trichophyton rubrum* (MIC of 500 µg/mL) and *T. mentagrophytes* (MIC of 250 µg/mL)	Tangarife-Castaño et al. (2014)
	P. multiplinervium	3-farnesyl-2-hydroxy benzoic acid	Antibacterial activity against *S. aureus* (MIC of 12.5 µg/mL), *K. pneumoniae* (MIC of 12.5 µg/mL), *M. smegmatis* (MIC of 12.5 µg/mL), *P. aeruginosa* (MIC of 6.25 µg/mL), and *H. pylori* activity (MIC of 3.75 µg/mL)	Rüegg et al. (2006)

P. obliquum	Obliquol A	Antibacterial activity against *E. coli* (MIC of 5.0 µg/mL) and *Staphylococcus epidermis* (MIC of 2.5 µg/mL)	Valdivia et al. (2008)
	Obliquol B	Antibacterial activity against *E. coli* (MIC of 5.0 µg/mL) and *Staphylococcus epidermis* (MIC of 5.0 µg/mL)	Valdivia et al. (2008)
P. tuberculatum Jacq.	*cis*-Piplartine	Antifungal activity against *C. cladosporioides* (MAR of 5 µg)	Vasques et al. (2002)
	Fagaramide	Antifungal activity against *C. cladosporioides* (Minimum amount required, MAR, of 5 µg)	Vasques et al. (2002)
	Methyl-*trans*-6,7,8-trimethoxycinnamate	Antifungal activity against *C. cladosporioides* (MAR= 5 µg)	Vasques et al. (2002)
	Methyl-6,7,8-trimethoxydihydrocin-namate	Antifungal activity against *C. cladosporioides* (MAR= 10 µg)	Vasques et al. (2002)
	Essential oil (fruits)	Antifungal activity against *Cladosporium sphaerospermum* (MIC of 10 µg)	Navickiene et al. (2006)
	Dicloromethane/metha-nol extract (infloscence)	Antifungal activity against *Trichophyton rubrum* (Concentration of100	Palacios et al. (2009)

			µg/mL)	
		Ethanol extract (leaves)	Antifungal activity against *Trichophyton rubrum* (Concentration of 500 µg/mL)	Palacios et al. (2009)
		Essential oil (leaves)	Antifungal activity against *Candida albicans*, *C. krusei*, *C. neoformans* and *C. parapsilosis* (Concentration of 1000 µg/mL)	Morandim-Giannetti et al. (2010)
	P. umbellatum	Hydroethanol extract (leaves)	Antibacterial activity against *Salmonella typhimurium*, *Shigella flexneri* and *Enterococcus faecalis* (MIC of 12.5 µg/mL)	da Silva et al. (2014)
Anticancer and anti-inflammatory activities	*P. aduncum*	Dillapiole	The compound showed anti-inflammatory activity using the carrageenan-induced edema, after 2 hours (17%)	Parise-Filho et al. (2011)
	P. amalago	Chloroform extract (leaves)	Anti-inflammatory activity against the Croton oil-induced ear oedema in mice (ID_{50} of 498 µg/cm^2)	Sosa et al. (2002)
	P. fimbriulatum C.DC.	Diayangambin	The compound reduced *in vitro* the production of prostaglandin E2 at 10 µM in stimulated RAW macrophage cell line. Furthermore, a reduction of ear swelling was seen after oral administration	De Leon et al. (2002)

			(Concentration of 40 mg/kg) of the compound to 2,4-dinitrofluorobenzene treated mice	
	P. obliquum	Obliquol B	The compound exhibited a IC_{50} closed to 5.0 μM in the NF-κB-dependent luciferase gene reporter assay	Valdivia et al. (2008)
	P. umbellatum	Dichloromethane extract (leaves)	The extract displayed antiproliferative activity, by reduction of Ehrlich solid tumor growth at 38.7 and 52.2% oral administration (200 and 400 mg/kg respectively) Anticancer activity. It inhibited the growth of melanoma, glioma, lung, prostate, kidney and ovarian human tumor cell lines *in vitro* (GI_{100} between 6.8 and 14.9 μg/mL)	Iwamoto et al. (2015)
Antidiabetic activity	*P. auritum*	Hexane extract (leaves)	Antidiabetic activity decreased the levels of blood glucose. The administration of 200 and 400 mg/kg of the extract increased serum and pancreas tissue insulin	Gutierrez (2012)
Antiulcer and gastric antisecretory effects	*P. tuberculatum*	Piplartine	Inhibited gastric ulcers by 80% at a dose of 4.5 mg/kg.	Burci et al. (2013)
	P. umbellatum	Hydroethanolic extract (leaves)	Gastroprotective activity reduced gastric lesions at 30, 100 and 300 mg/kg in a not dose dependent way.	da Silva et al. (2016)
Antiparasitic	*P. aduncum*	2',6'-dihydroxy-4'-	Activity against	Torres-

Activity	methoxychalcone	*Leishmania amazonensis:* promastigotes (ED_{50} of 0.5 µg/mL); and amastigotes (ED_{50} of 24 µg/mL)	Santos et al. (1999)
	2,2-dimethyl-2*H*-chromene-6-carboxylic acid	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 558.3 µM)	Batista et al. (2008)
	Methyl-2,2-dimethyl-2*H*- chromene-6-carboxylate	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 190.1 µM)	Batista et al. (2008)
	Methyl-8-hydroxy-2,2-dimethyl- 2*H*-chromene-6-carboxylate	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 44.8 µM)	Batista et al. (2008)
	Methyl-2,2-dimethyl-8-(3'- methylbut-2'-enyl)-2*H*-chromene-6-carboxylate	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 33.2 µM)	Batista et al. (2008)
	3-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-benzoic acid	Antiparasitic activity, strongly inhibited the grow of *L. braziliensis* (IC_{50} 6.5 µg/mL)	Flores et al. (2009)
	4-hydroxy-3-(3-methyl-1-oxo-2-butenyl)-5-(3-methyl-2-butenyl) benzoic acid	Antiparasitic activity against promastigotes of *L. amazonensis*, *L. braziliensis* and *L. donovani* (IC_{50} = 17.8 µg/mL); exhibited moderate activity against epimastigote of *T. cruzi* (IC_{50} = 16.5 µg/mL)	Flores et al. (2009)
	Dichloromethane extract (leaves)	Antiparasitic activities against *T. cruzi* (IC_{50} = 38 µg/mL); chloroquine-resistant *P. falciparum* (IC_{50} = 21 µg/mL); and *L.*	Calderón et al. (2010)

		mexicana (IC_{50} > 50 µg/mL)	
	5-prenylated dihydrochalcone	Antileishmanial activity on promatigote forms of *L. amazonensis* (EC_{50} of 11.03 µM), *L. braziliensis* (EC_{50} of 26.70 µM), and *L. chagasi* (EC_{50} of 11.26 µM)	Dal Picolo et al. (2014)
P. amalago	N-[7-(3',4'-methylenedioxyphenyl)-2(*E*),4(*E*)-heptadienoyl] pyrrolidine	Antiparasitic activity against the promastigote form of *L. amazonensis* (IC_{50} = 15 µM)	Carrara et al. (2013)
	N-[7-(3',4'-methylenedioxyphenyl)-2(*Z*),4(*Z*)-heptadienoyl] pyrrolidine	Antiparasitic activity against the promastigote form of *L. amazonensis* (IC_{50} = 20 µM); and caused a complete mortality of adult worms of *S. mansoni* (Concentration of 100 µM)	Carrara et al. (2013); Carrara et al. (2014)
P. arboreum	Hexane fractions (leaves)	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 13.3 µg/mL)	Regasini et al. (2009b)
	Hexane fractions (fruits)	Antitrypanocidal activity against *T. cruzi*, inhibition on the epimastigote (IC_{50} = 31.3 µg/mL)	Regasini et al. (2009b)
P. auritum	Essential oil (aerial parts)	Antileishmanial activity against the promastigotes of *L. major* (IC_{50} of 29.1 µg/mL), *L. mexicana* (IC_{50} of 63.3 µg/mL), *L. braziliensis* (IC_{50} of 52.1 µg/mL), and *L. donovani* (IC_{50} of	Monzote et al. (2010)

		12.8 µg/mL)	
P. bogotense	Essential oil (aerial parts)	Antiparasitic activity against epimastigotes of *T. cruzi* (IC_{50} = 10.09 µg/mL)	Leal et al. (2013)
P. bogotense, *P. bredemeyeri*, P. *marginatum* and *P. septuplinervium* (Miq.) C.DC.	α-Pinene	Antiparasitic activity against the epimastigote form of *T.cruzi* (IC_{50} = 2.74 µg/mL), the amastigote form of *T.cruzi* (IC_{50} = 1.92 µg/mL), and the promastigote form of *L. infantum* (IC_{50} = 45.94 µg/mL).	Leal et al. (2013)
P. bogotense, *P. bredemeyeri*, *P. marginatum*	Limonene	Antiparasitic activity on the epimastigote form of *T.cruzi* (IC_{50} = 38.71 µg/mL)	Leal et al. (2013)
P. bogotense, *P. bredemeyeri*, *P. marginatum* and *P. septuplinervium*	*trans*-β-Caryophyllene	Antiparasitic activity against the epimastigote (IC_{50} = 2.89 µg/mL) and amastigote (IC_{50} = 24.54 µg/mL) forms of *T.cruzi*; and on the promastigote (IC_{50} = 24.02 µg/mL) and amastigote (IC_{50} = 53.39 µg/mL) forms of *L. infantum*	Leal et al. (2013)
P. crassinervium	1,4-dihydroxy-2-(3',7'-dimethyl-1'-oxo-2'- *E*-6'-octadienyl) benzene	Antitrypanosomal activity against *T. cruzi* (IC_{50} = 6.10 µg/mL)	Lopes et al. (2008)
P. cumanense	Ethanol extract (fruits and leaves)	Antimalarial activity *Plasmodium falciparum* chloroquine resistant strain < 1 µg/mL for both extracts	Garavito et al. (2006)
P. dilatatum	Dichloromethane	Antiparasitic	Calderón

		extract (leaves)	activities against *T. cruzi* (IC_{50} = 31 µg/mL); chloroquine-resistant *P. falciparum* (IC_{50} = 12 µg/mL); and *L. mexicana* (IC_{50} > 50 µg/mL)	et al. (2010)
	P. hispidum	Petrol ether/ethyl acetate extract (air dried branches and leaves)	Antimalarial activity against *P. falciparum* sensitive to chloroquine (IC_{50} of 7.6 µg/mL) and resistant to chloroquine (IC_{50} of 13.0 µg/mL)	Jenett-Siems et al. (1999)
		2',4,6'-trihydroxy-4'-methoxydihydrochal-cone	Antiplasmodial activity for *P. falciparum* sensitive to chloroquine, (16.9 µg/mL) and resistant to chloroquine (10.4 µg/mL)	Jenett-Siems et al. (1999)
		Dichloromethane extract (leaves)	Antiparasitic activities against *T. cruzi* (IC_{50} = 26 µg/mL), chloroquine-resistant *P. falciparum* (IC_{50} = 22 µg/mL), and *L. mexicana* (IC_{50} > 50 µg/mL)	Calderón et al. (2010)
	P. marginatum	Essential oil (aerial parts)	Antiparasitic activity against epimastigotes of *T. cruzi* (IC_{50} = 16.15 µg/mL)	Leal et al. (2013)
	P. peltatum	4-nerolidylcatechol	Antimalarial activities *in vivo* against *P. berghei* was evaluated using the 4-day Peter's suppression test on Webster Swiss albino mice. Significant	Rocha E Silva et al. (2011)

		chemosuppression of the parasites was displayed after oral administration at 600 mg/kg/day on days 5 and 7 (63.1% and 59.7% respectively). *In vitro* antimalarial activity was assessed on standard and field *P. falciparum* strains (IC_{50} between 0.05 and 2.11 µg/mL)	
P. septuplinervium	Essential oil (aerial parts)	Antiparasitic activity against epimastigotes of *T. cruzi* (IC_{50} = 13.98 µg/mL); and promastigote form of *L. infantum* (IC_{50} = 30.05 µg/mL)	Leal et al. (2013)
P. tuberculatum	Hexane fractions (leaves)	Antitrypanocidal activity against *T. cruzi* (IC_{50} = 17.2 µg/mL)	Regasini et al. (2009b)
	Hexane fractions (fruits)	Antitrypanocidal activity against *T. cruzi* inhibition on the epimastigote (IC_{50} = 32.2 µg/mL)	Regasini et al. (2009b)
	Plipartine	Antiparasitic activity against *P. falciparum* (IC_{50} = 3.2 µg/mL), (SI = 72.5); *L. amazonensis* (IC_{50} = 179.0 µg/mL) promastigotes form of *L. amazonensis* (SI = 1.3).	Araújo-Vilges et al. (2017)
P. umbellatum	Ethanol extract (leaves)	Antiparasitic activity against *T. cruzi* (IC_{50} = 25 µg/mL), *P. falciparum* (IC_{50} > 50 µg/mL), and *L. Mexicana* (IC_{50} > 50 µg/mL)	Calderón et al. (2010)

Diuretic Activity	*P. amalago*	Ethanol extract (leaves)	Oral administration of the extracts to Wistar rats (125 mg/kg) induced the most potent diuretic activity (diuretic index of 1.54)	Novaes et al. (2014)
Estrogenic and Serotonergic Activity	*P. hispidum*	Ethanol extract (leaves)	Estrogenic activity *in vitro* using ER_{β} receptor assay (76%) (100 µg/mL). Serotonergic activity *in vitro* through the $5\text{-}HT_{1A,5A,7}$ (Concentration of 50 µg/mL)	Michel et al. (2007)
		9,10-methylenedioxy-5,6-*Z*-fadyenolide	Serotonergic activity, bounding to the $5\text{-}HT_{1A}$ (IC_{50} of 16.1 µM) and $5\text{-}HT_{7}$ (IC_{50} of 8.3µM) receptors	Michel et al. (2010)
Inhibitory Effects towards Phospholipases A_2	*P. peltatum* and *P. umbellatum*	4-nerolidylcatechol	Inhibition of myotoxin I, with an inhibitor-toxin ratio of 10:1, and (IC_{50} aprox. 1.0 mM)	Núñez et al. (2005)
Insecticidal Activity	*P. aduncum*	Dillapiole	Insecticidal activity against pupae and larvae of *A. aegypti*	Rafael et al. (2008)
	P. aduncum, *P. arboreum* and *P. marginatum*	Essential oils (leaves)	Larvicidal activity against *A. aegypti*, *P. aduncum* (LC_{50} = 46 ppm) *P. arboreum* (LC_{50} = 55 ppm), and *P. marginatum* (LC_{50} = 34 ppm)	Santana et al. (2015)
	P. hispidum and *P. longispicum* C.DC.	Essential oils (leaves)	The larvicidal activity against *A. aegypti* (Concentration of 250 µg/mL)	Santana et al. (2016)
	P. marginatum	Essential oil (leaves)	Larvicidal activity against *A. aegypti*	Autran et al. (2009)

			(LC_{50} =23.8 ppm)	
		Essential oil (stem)	Larvicidal activity against *A. aegypti* (LC_{50} =14.3 ppm)	Autran et al. (2009)
		Essential oil (inflorescense)	Larvicidal activity against *A. aegypti* (LC_{50} =19.9 ppm)	Autran et al. (2009)
Local anesthetic activity	*P. darienense*	Pipercallosine	Higher local anesthetic activity (2%) in Guinea pig wheal method than lidocaine	Rodriguez et al. (2005)

Abbreviations: **ED_{50}:** Effective dose concentration; **GI_{100}:** 100% growth inhibition; **IC_{50}:** Half maximal inhibitory concentration; **LC_{50}:** 50% Lethal concentration; **MIC:** Minimum inhibitory concentration; **MAR:** Maximum amount required