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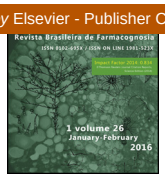

Review

Folk medicine, phytochemistry and pharmacological application of *Piper marginatum*

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ABSTRACT

Piper marginatum Jacq., Piperaceae, is a widely distributed Neotropical species abundant in the Caribbean, exhibiting a characteristic winged petiole and a heart-shaped leaf, its two vegetative landmarks for rapid identification. The species has been employed by traditional indigenous cultures for its reputed medicinal properties. The plant is most frequently employed by local healers in Central America, the Antilles and South America, for alleviating gastrointestinal ailments, administered as a decoction or infusion for its tonic, diuretic and carminative effects. These beneficial properties may be attributed to the presence of various phytochemicals within *P. marginatum*, with most of the studies focusing on the essential oil of the plant. Monoterpenoids, sesquiterpenoids and phenylpropanoids of a varied chemical structure have been identified in the essential oil, while phenylalkanoids, aristolactams, amides and flavonoids have been purified by chromatographic techniques from the extracts. The biological and pharmacological examination of *P. marginatum* showed that the plant may be a valuable source of mosquitocidal, antifungal, antitumoral and hemostatic agents. Future bioguided research may yield biologically relevant molecules useful in medicine or agriculture.

Introduction

The species *Piper marginatum* Jacq., Piperaceae, was first described in 1781 by Dutch botanist Nikolaus Joseph von Jacquin. The species had been collected during excursions to Central and South America, and the morphological characters were recorded as heart-shaped, acuminated, multi-veined and reticulated leaves, with a marginal, grooved and winged petiole, and solitary flowers (Jacquin, 1786). The Swiss botanist Anne Casimir Pyrame de Candolle was the first to observe small morphological differences between different collections of *P. marginatum*, and recognized three subspecies: *P. marginatum* Jacq, *P. marginatum* var. *anisatum* (Kunth) C.DC. and *P. marginatum* var. *catalpifolium* (Kunth) C.DC. (Candolle, 1902). In the comprehensive work "The Piperaceae of Northern South America", William Trelease and Truman G. Yuncker, differentiated the subspecies based on the puberulent (var. *anisatum*) or pillose (var. *catalpifolium*) nature of the nerves on the upper surface of the leaves (Trelease and Yuncker, 1950). However the difficulty to characterize specimens at the subgenus level given its extensive homoplasy (the development of similar characters by parallel or convergent evolution) was recognized by Ricardo Callejas (Callejas, 1986), and thus the modern classifications consider the subspecies as synonyms of *P. marginatum* Jacq. (Andrade et al., 2008). In this work, the *sensu lato* of *P. marginatum* was considered, following the criteria of the Missouri Botanical Garden (Tropicos.org, 2015), which collates under *P. marginatum* several species and subspecies, including *Piper san-joseanum* C. DC., *Piper patulum* Bertol., *Piper uncatum* Trel., *Piper quiriguanum* Trel., among others.

The phylogenetic analysis of the genus *Piper* using the sequence alignment of the internal transcribed spacer (ITS) of the 18S-26S nuclear ribosomal DNA and the chloroplast intron region *psbJ*-petA, indicated that the species *P. marginatum* is closely related to *P. multiplinervium* and *P. schwakei*, and together these three species build the *P. marginatum* complex (Jaramillo et al., 2008). Moreover the Pothomorphe group species (which includes *P. auritum*, *P. peltatum* and *P. umbellatum*) showed to be phylogenetically related to the *P. marginatum* complex.

The species *P. marginatum* has been widely recognized for its medicinal purposes within a number of indigenous cultures located in the Caribbean and Amazon regions, from Central America and the Antilles to Brazil (de Núñez and Johnson, 1943; Braga, 1960; D'Angelo et al., 1997; Di Stasi and Hiruma-Lima, 2002). In addition the dried leaves have been used as a natural sweetener (Hussain et al., 1990; Surana et al., 2006). Its major secondary metabolites are terpenoids and phenylalkanoids (Andrade et al., 2008).

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In addition a number of biological and pharmacological published data (Sequeda-Castañeda et al., 2015) seems to support its use in traditional medicine. This review covers the ethnomedicinal, phytochemical and biological literature published on *P. marginatum* with the aim to identify the research voids for future investigation and critically assess the potential application of the species in medicine and agriculture.

Folk medicine and traditional uses

The indigenous communities in Central America, the Antilles and South America repeatedly reported to use *P. marginatum* for treating a varied array of diseases and ailments. Gastrointestinal problems are the most common therapeutic use in the traditional medicine, spanning different locations and cultures (Fig. 1, Box 1). The plant is recurrently employed either as a decoction or infusion for its tonic, diuretic and carminative effects (Foungbe et al., 1976; Johnson, 1998; Di Stasi and Hiruma-Lima, 2002; de Albuquerque et al., 2007). It is also used to treat gallbladder, liver, stomach, spleen, urinary and gastrointestinal ailments (van den Berg, 1982; Pereira et al., 2011; Yukes and Balick, 2011), but also dysentery (de Núñez and Johnson, 1943). In Central America, the species is known as "Aniseto" and it is employed as an infusion for treating flatulence disorders, in a similar way to star anise.

Pain relief is the second most frequent use of *P. marginatum* in the traditional medicine (Fig. 1, Box 1). The plant is used to relieve toothache, headaches and pain caused by itching, and as a general analgesic (Hazlett, 1986; Giraldo Tafur, 1996; Di Stasi and Hiruma-Lima, 2002; Pereira et al., 2011). The plant is employed topically as a cataplasm to alleviate the pain of the limbs or abdomen, or as a decoction or infusion for teeth, head and stomach aches (García, 1974; Giraldo Tafur, 1996; Yukes and Balick, 2011).

The species *P. marginatum* is also commonly used as a hemostatic (Fig. 1, Box 1). The plant has been reported to stop bleeding particularly in the case of ophidian accidents (de Núñez and Johnson, 1943; Braga, 1960; D'Angelo et al., 1997; Sánchez et al., 2011; Ortega-Galvan, 2014). Reports of the topical application of the plant to alleviate itching and scratching from insect bites including ants (Elisabetsky and Gely, 1987) has been recurrently reported (Box 1), and it remains to be determined if this property is due solely to the analgesic effect. In addition *P. marginatum* displays antimicrobial properties with recorded applications in Brazil (Corrêa and Pena, 1984; D'Angelo et al., 1997), Colombia (Duke and Vasquez, 1994), Cuba (Sánchez et al., 2011) and Puerto Rico (de Núñez and Johnson, 1943). The species is also employed to treat female disorders, skin problems and insect bites (van Andel et al., 2008; Lans and Georges, 2011; Pereira et al., 2011). In Suriname, Trinidad and Puerto Rico, the plant is widely used to treat female disorders such as to clean female sexual organs, to help parturition, and to reduce the menstruation flow, respectively (Morton, 1977; van Andel et al., 2008; Lans and Georges, 2011). In the French Guiana, *P. marginatum* is used to treat cutaneous eruptions and skin rashes (Foungbe et al., 1976; Morton, 1977; D'Angelo et al., 1997), and in Brazil it is used to alleviate hitching caused by insect bites (Pereira et al., 2011).

Phytochemistry

The species *P. marginatum* shows a distinct phytochemistry with the presence of specific secondary metabolites, not found in other *Piper* species. For instance, *P. marginatum* is the only *Piper* species containing anethole, estragole, isoeugenol methyl ether, the phenylalkanoids 3-farnesyl-4-hydroxybenzoic and 3-farnesyl-4-methoxybenzoic acids and the glycosides marginatoside and vitexin (Parmar et al., 1997). No other *Piper* species have shown the presence of these chemotaxonomic markers.

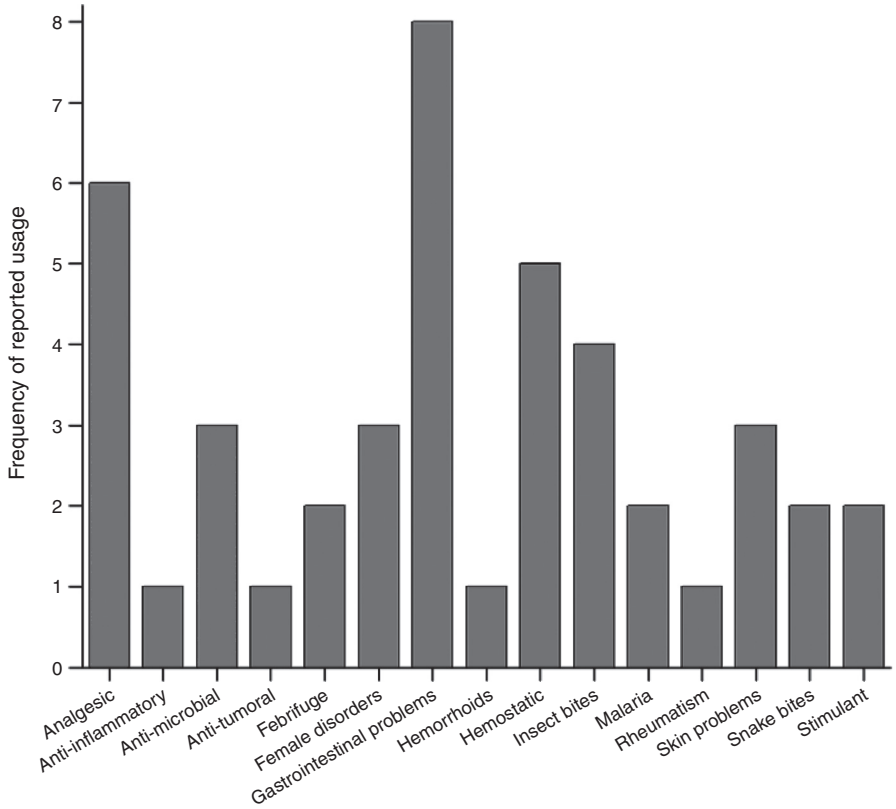


Fig. 1. Frequency of application of *Piper marginatum* in the traditional medicine based on the type of ailment to treat.

Box 1
Traditional medicine applications of *Piper marginatum* by local communities.

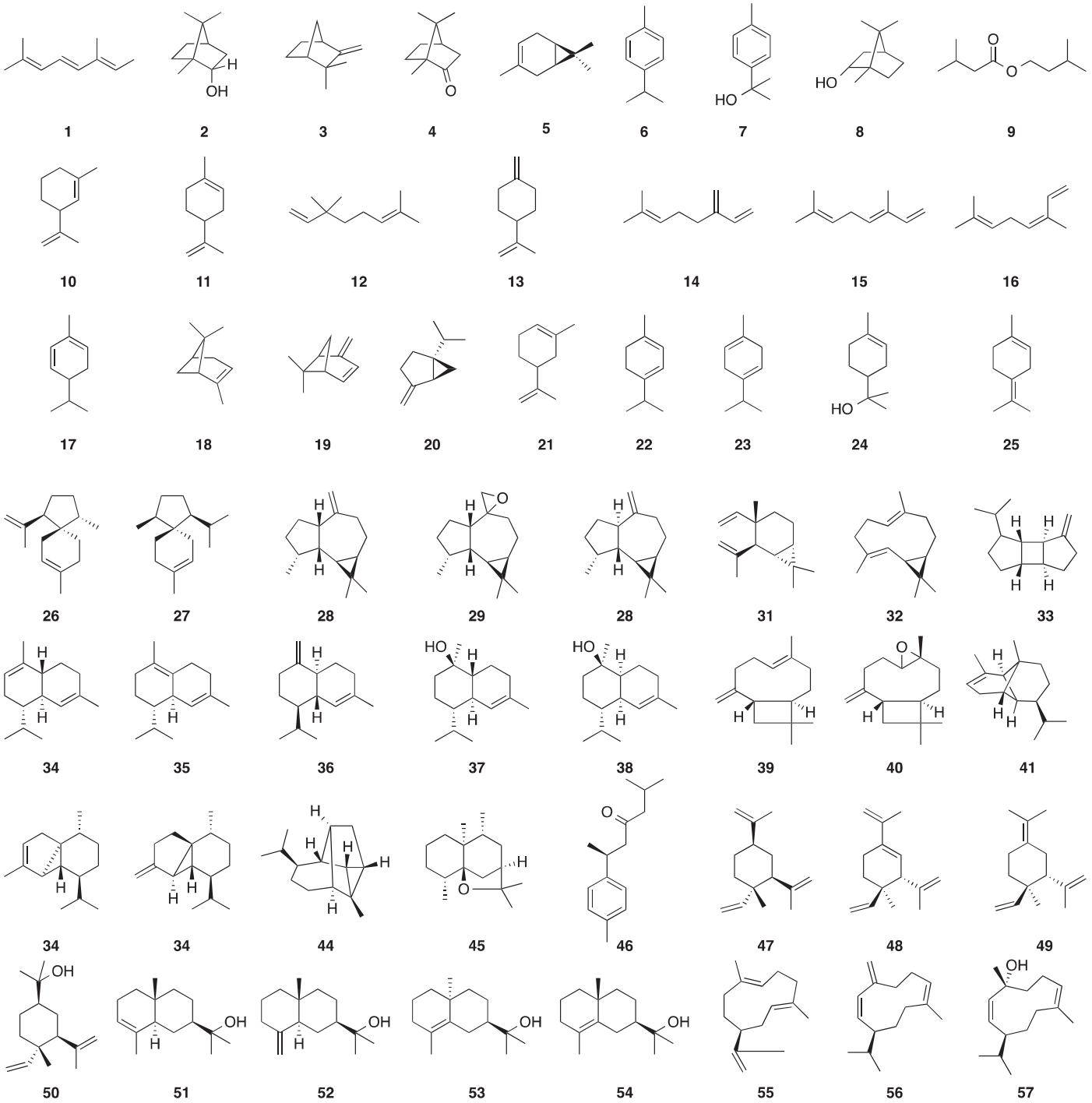
Location	Organ of the plant	Medicinal properties, or afflictions treated	Mode of application	References
Amazon region	Roots	Carminative, diuretic, tonic, useful against toothache and cobra venom	Baths	Di Stasi and Hiruma-Lima (2002)
	Roots	To alleviate pain and itching of insect bites	Cataplasm	
	Fruits and leaves	Stimulant	nd	
	Stem, leaves	Against itching from ant bites	Cataplasm	Elisabetsky and Gely (1987)
	nd	As antispasmodic and against liver and gallbladder diseases	Decoction	van den Berg (1982)
Brazil	Leaves	Rheumatism, bleeding skin wounds, toothache and tumors	Decoction	Corrêa and Pena (1984), D'Angelo et al. (1997)
	Leaves	To reduce swellings	Rubbed with fat as cataplasm, poultice	Branch and Silva (1983), Duke and Vasquez (1994)
	Roots	To alleviate hitching caused by insect bites, and also as a teeth pain reliever	Maceration	Pereira et al. (2011)
	Leaves and fruits	As antispasmodic, to treat cough, and affections of the spleen, liver and intestinal problems	Used topically	Pereira et al. (2011)
	Stem, leaves, roots	Against high blood pressure, asthma, erysipelas, problems with urinary system and as a diuretic	nd	de Albuquerque et al. (2007)
	nd	To treat hemorrhoids	Infusion	Rodrigues and Andrade (2014)
	nd	Hemostatic, snake-bite medicine	nd	Braga (1960), D'Angelo et al. (1997)
Colombia	Leaves, stem	For protecting teeth against cavities	Chewed	Duke and Vasquez (1994), García (1974)
	Leaves	Analgesic	Infusion and cataplasm	Giraldo Tafur (1996)
	Roots	Used against malaria and as stimulant	Juice	García (1974)
	Entire plant	To reduce fevers	Decoction	García (1974)
Costa Rica	Leaves	To treat headaches	Decoction	Hazlett (1986)
Cuba	nd	Antiseptic, astringent, antihemorrhagic and hemostatic	nd	Sánchez et al. (2011)
Dominican Republic	Leaves	Indigestion and flatulence disorders but also against stomach pain	Infusion	Yukes and Balick (2011)
French Guiana	Leaves	Used in combination with *Quassia amara* to treat malaria	Decoction	Vigneron et al. (2005)
	Leaves	To treat cutaneous eruptions and insect bites	Decoction	Foungbe et al. (1976)
	Roots	Diuretic and sudorific	Infusion	Foungbe et al. (1976)
	nd	Used to treat skin rashes	nd	D'Angelo et al. (1997), Morton (1977)
Panama	nd	Carminative, diuretic, emmenagogue, hemostatic	nd	Johnson (1998)
	nd	Reduce fever and lung secretions	nd	D'Angelo et al. (1997), Morton (1977)
Puerto Rico	Leaves	Hemostatic	Cataplasm	de Núñez and Johnson (1943)
	Leaves	As treatment to dysentery	Infusion	de Núñez and Johnson (1943)
	nd	Reduces menstruation flow	nd	Morton (1977)
Suriname	Leaves	To cleanse the vagina, cleanse the uterus, disguise bad smell, enhance sexual pleasure amongst other applications	Steam bath	van Andel et al. (2008)
Trinidad and Tobago	nd	To help parturition	Infusion or decoction drank	Lans and Georges (2011)

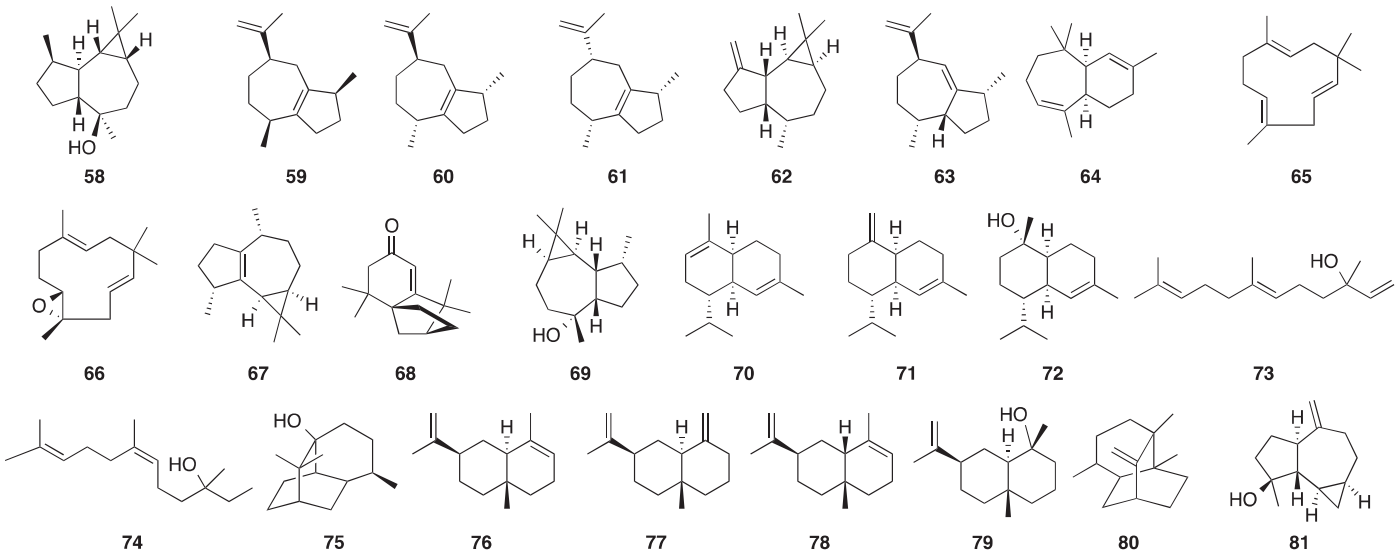
nd refers to no data.

According to the essential oil (EO) components, seven chemotypes were recognized by Andrade et al. in their comprehensive study with 22 samples of *P. marginatum* collected throughout the Brazilian Amazon (Andrade et al., 2008). The existence of seven chemotypes may induce to consider the assumption of ancient character of *P. marginatum*, allowing potential speciation events to occur during recent evolution. This hypothesis may be tested in the future by molecular phylogenetic analysis. The composition of the EO of the leaf, stem and inflorescence from a *P. marginatum* species collected in near Recife, Brazil, showed that the major component was (*Z*)-asarone (30.4%) on the EO of the leaf, (*E*)-asarone (32.6%) on the EO of the stem, and patchoulol (23.4%) on the EO of the inflorescence (Autran et al., 2009). A *P. marginatum* species from Costa Rica (Vogler et al., 2006) was rich in anethole (45.9%) and anisaldehyde (22.0%), while *P. marginatum* collected near Guantanamo in Cuba (Sánchez et al., 2011) showed high amounts of isosafrole (37.3%) and nothosmyrnol (22.7%). Moreover, the EO obtained from *P. marginatum* collected near Acandi, Colombia, had high concentration of anethole (46.3%) followed by estragol (28.9%), whereas the same species collected in Turbaco, Colombia, showed

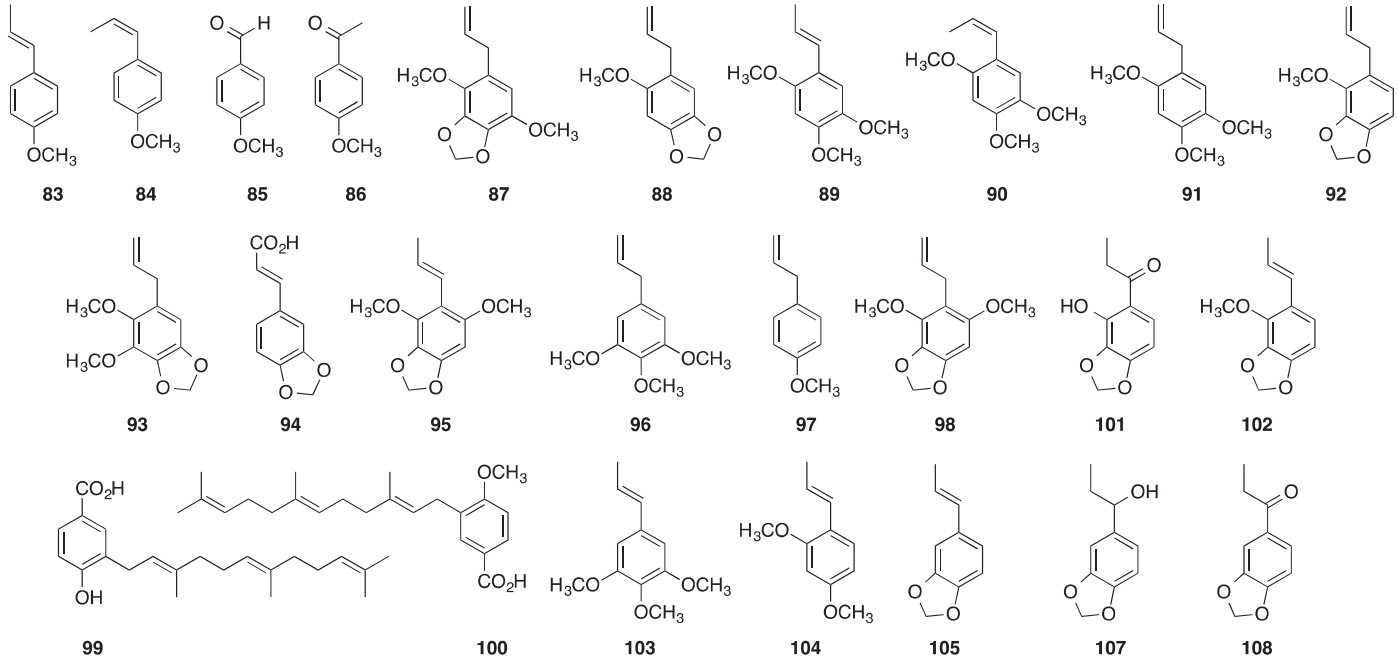
an EO rich in germacrene D (36.6%) (Jaramillo-Colorado et al., 2015). These studies suggest that there are more than seven chemotypes on the EO of *P. marginatum sensu lato*. These results point out to a dramatic variation in chemical composition for a set of related marginatum-phenotype species but in addition it is necessary to consider the variability associated to chronobiological phenomena (monthly, weekly and daily variation) as hypothesized by Moraes et al. (2014).

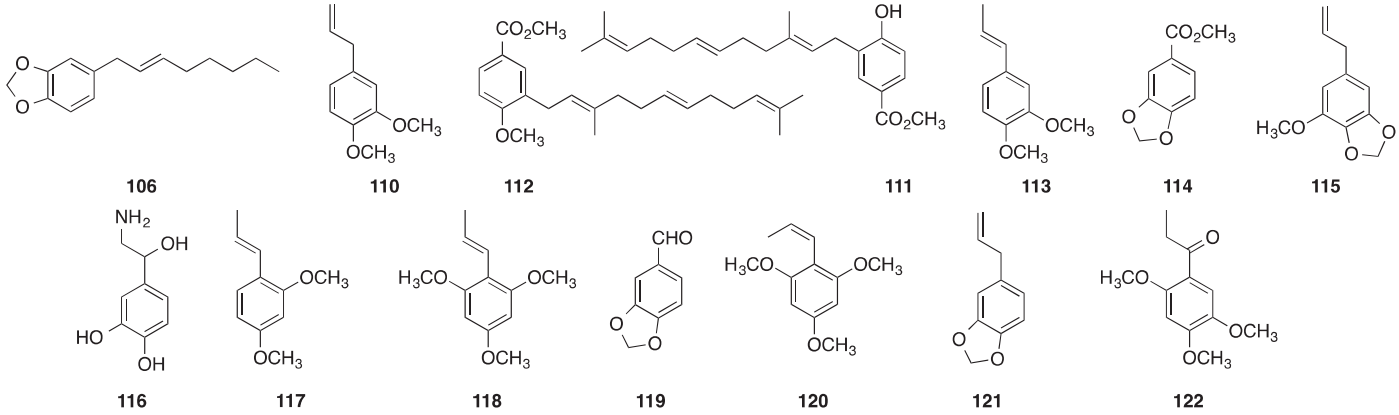
Most of the phytochemical studies on *P. marginatum* have been carried out on the EO of the plant. Twenty five monoterpen(e)-oids (**1–25**, Box 3), and fifty seven sesquiterpen(e)-oids (**26–82**, Box 3) have been identified from the EO of *P. marginatum* species collected in different locations, at different moments and studied under different conditions. Thus there are reasons to explain the variation observed on the chemical composition of the EO differentiated in seven chemotypes (Andrade et al., 2008). But in addition to this variability, the assembly of previously described subspecies collated under the *sensu-lato* name *P. marginatum* may contribute to the notable chemical variation, as each subspecies may have a different secondary metabolism. It remains to be verified if the populations ascribed as *P. marginatum* are undergoing speciation events, moreover considering its widespread geographical distribution.



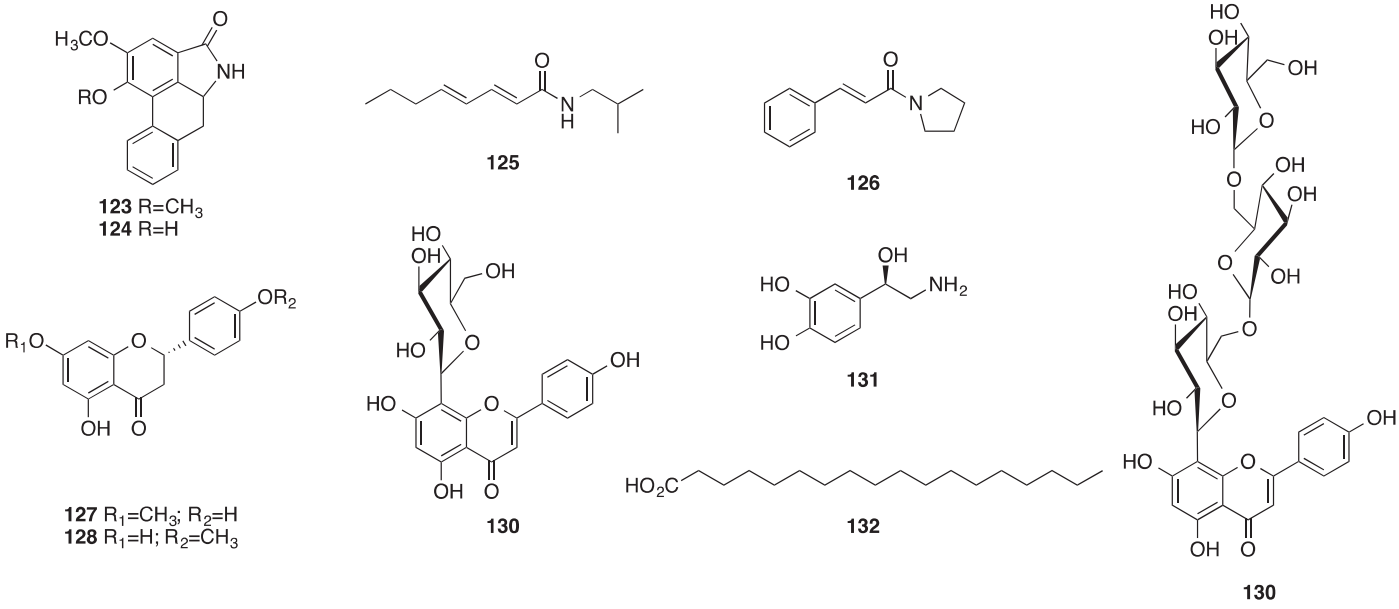


The sole sesquiterpenoid which has been purified using chromatographic techniques is caryophyllene oxide (**40**) (de Oliveira Chaves and de Oliveira Santos, 2002). Among the thirty-nine phenylalkanoids (**83–122**, Box 2) reported for *P. marginatum*, most of them were identified by CG-MS analysis of the EO of the plant, while some of them were isolated to purity by chromatographic techniques (apiol (**87**), (*E*)-asarone (**89**), croweacin (**92**), 2,6-dimethoxy-3,4-methylenedioxy-1-(2-propenyl)-benzene (**95**), 3-farnesyl-4-hydroxybenzoic acid (**99**) and 3-farnesyl-4-methoxybenzoic acid (**100**), 2-hydroxy-3,4-methylenedioxypropiophenone (**101**), marginatine (**106**), 3,4-methylenedioxypropiophenone (**108**), 2-methoxy-4,5-methylenedioxypropiophenone (**109**), pipermargine (**118**) piperonal (**119**), 1-(1-(*Z*)-propenyl)-2,4,6-trimethoxybenzene (**120**), safrole (**121**), 2,4,5-trimethoxypropiophenone (**122**)) (de Diaz and Gottlieb, 1979; Maxwell and Rampersad, 1988; de Oliveira Santos et al., 1997; Santos et al., 1998; de Oliveira Santos and de Oliveira Chaves, 1999b; de Oliveira Chaves and de Oliveira Santos, 2002).





The alkaloids or amides so far identified from *P. marginatum* are the aristolactams cepharanone B (**123**) and piperolactam A (**124**), (*E*,*E*)-*N*-isobutyl-2,4-octadienamide (**125**) and cinnamoyl pirrolidide (**126**) (de Oliveira Santos and de Oliveira Chaves, 1999a; de Oliveira Chaves et al., 2003; de Oliveira Chaves et al., 2006). Two flavanones 5,4′-dihydroxy-7-methoxyflavanone (**127**) and 5,7-dihydroxy-4′-methoxyflavanone (**128**), and two flavonoid glycosides marginatoside (**129**) and vitexin (**130**) have been isolated from the leaves of *P. marginatum* (Tillequin et al., 1978; Reigada et al., 2007). The catecholamine noradrenaline (**131**) was identified by high performance liquid chromatography (D'Angelo et al., 1997), and the fatty acid stearic acid (**132**) has been purified from the leaves (de Diaz and Gottlieb, 1979).



Biological and pharmacological applications

The sweetening effect of the plant recorded in the traditional application was attributed to the presence of (*E*)-anethole (**83**), a sweet phenylpropanoid and major compound in certain chemotypes of the EO of *P. marginatum* but also present in fennel (*Foeniculum vulgare*), star anise (*Illicium verum*), cicely (*Myrrhis odorata*) and anise root (*Osmorhiza longistylis*) (Hussain et al., 1990). (*E*)-Anethole has been reported to provide protection against chemically-induced apoptosis and genotoxicity (Abraham, 2001; Galicka et al., 2014), and to be non-carcinogenic in mice (Miller et al., 1983) posing no risk to human health (Newberne et al., 1999).

Most studies evaluating the biological and pharmacological properties of *P. marginatum* have focused on the essential oil (Box 3). The leaf EO demonstrated growth inhibition of *Escherichia coli* bacteria with a minimum inhibitory concentration (MIC) value between 700 and 900 μg/ml against two pathogenic strains STEC0157 and EPEC0312 respectively (Duarte et al., 2007). A much lower MIC value of 120 μg/ml was found against the phytopathogenic bacterium *Xanthomonas albilineans* (Sánchez et al., 2012). The leaf EO was also screened for fungal inhibition against both *Alternaria solanii* and *Fusarium oxysporum*, displaying moderate activity in disk diffusion assays (dos Santos et al., 2011; Duarte et al., 2013). However another study reported that the EO from *P. marginatum* was inactive against *F. oxysporum* with an MIC value higher than 500 μg/ml, while it was found to be slightly more active against *Trichophyton rubrum* and *Trichophyton mentagrophytes* with respective MIC values of 500 and 250 μg/ml (Tangarife-Castaño et al., 2014). Moreover both the EO and the ethanolic extract of *P. marginatum* were reported to be inactive against *Candida albicans* with MIC values higher than 2.0 mg/ml (Duarte et al., 2005). The EO obtained from the leaf, steam and flower of *P. marginatum* were tested for activity against *Aedes aegypti*, and found to be potent larvicidal mixtures (LC_{50} ranging from 19.9 to 23.8 μg/ml) with the EO

Box 2
Reported phytochemicals identified in *Piper marginatum*.

Class	Compound	Present in organ	Reference
Monoterpene and monoterpenoids	Allocymene (**1**)	Leaf, stem	Ramos et al. (1986)
	Borneol (**2**)	Leaf	Andrade et al. (2008)
	Camphene (**3**)	Leaf	Andrade et al. (2008)
	Camphor (**4**)	Leaf	Andrade et al. (2008)
	δ-3-Carene (**5**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986), Vogler et al. (2006)
	p-Cymene (**6**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Vogler et al. (2006)
	8-p-Cymenol (**7**)	Leaf, stem	Vogler et al. (2006)
	Isoborneol (**8**)	Leaf	Andrade et al. (2008)
	Isopentyl isovalerate (**9**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	Isosylvestrene (**10**)	Leaf	Andrade et al. (2008)
	Limonene (**11**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Vogler et al. (2006)
	Linalool (**12**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986), Vogler et al. (2006)
	p-Mentha-1-(7),8-diene (**13**)	Leaf	Andrade et al. (2008)
	Myrcene (**14**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	(*E*)-β-ocimene (**15**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	(*Z*)-β-ocimene (**16**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986)
	α-Phellandrene (**17**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	α-Pinene (**18**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	β-Pinene (**19**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986)
	Sabinene (**20**)	Leaf	Andrade et al. (2008)
	Sylvestrene (**21**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	α-Terpinene (**22**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	γ-Terpinene (**23**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	α-Terpineol (**24**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	α-Terpinolene (**25**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
Sesquiterpene and sesquiterpenoids	α-Acoradiene (**26**)	Leaf, inflorescence	Autran et al. (2009), Moraes et al. (2014)
	β-Acoradiene (**27**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	Alloaromadendrene (**28**)	Leaf	Andrade et al. (2008)
	Alloaromadendrene epoxide (**29**)	Leaf	Andrade et al. (2008)
	Aromadendrene (**30**)	Leaf	Andrade et al. (2008)
	Bicycloelemene (**31**)	Leaf	Sánchez et al. (2011)
	Bicyclogermacrene (**32**)	Leaf	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Sánchez et al. (2011)
	β-Bourbonene (**33**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	α-Cadinene (**34**)	Leaf	Moraes et al. (2014)
	δ-Cadinene (**35**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	γ-Cadinene (**36**)	Leaf, stem, inflorescence	Autran et al. (2009), Moraes et al. (2014)
	α-Cadinol (**37**)	Leaf	Andrade et al. (2008)
	δ-Cadinol (**38**)	Stem	Ramos et al. (1986)
	β-Caryophyllene (**39**)	Leaf, stem, inflorescence	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986)
	Caryophyllene oxide (**40**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), de Oliveira Chaves and de Oliveira Santos (2002)
	α-Copaene (**41**)	Leaf, stem, inflorescence	Andrade et al. (2008), Ramos et al. (1986), Autran et al. (2009), Moraes et al. (2014), Sánchez et al. (2011)
	α-Cubebene (**42**)	Leaf, stem, inflorescence	Andrade et al. (2008), Autran et al. (2009)
	β-Cubebene (**43**)	Leaf	Andrade et al. (2008)
	Cyclosativene (**44**)	Leaf	Andrade et al. (2008)
	β-Dihydroagarofuran (**45**)	Leaf	Andrade et al. (2008)
	ar-Dihydroturmerone (**46**)	Stem	Autran et al. (2009)
	β-Elemene (**47**)	Leaf, stem, inflorescence	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986), Sánchez et al. (2011)
	δ-Elemene (**48**)	Leaf, stem	Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986)
	γ-Elemene (**49**)	Leaf,	Ramos et al. (1986)
	Elemol (**50**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986), Sánchez et al. (2011)
	α-Eudesmol (**51**)	Leaf	Andrade et al. (2008), Sánchez et al. (2011)
	β-Eudesmol (**52**)	Leaf, stem	Bernal et al. (2011), Ramos et al. (1986), Andrade et al. (2008), Sánchez et al. (2011)
	10-*epi*-γ-Eudesmol (**53**)	Leaf	Andrade et al. (2008)
	γ-Eudesmol (**54**)	Leaf	Andrade et al. (2008)
	Germacrene A (**55**)	Leaf	Andrade et al. (2008)
	Germacrene D (**56**)	Leaf, inflorescence	Andrade et al. (2008), Autran et al. (2009)
	Germacrene D-4ol (**57**)	Leaf	Andrade et al. (2008)
	Globulol (**58**)	Leaf	Andrade et al. (2008)
	α-Guaiene (**59**)	Leaf, inflorescence	Autran et al. (2009), Moraes et al. (2014)

Box 2 (*Continued*)

Class	Compound	Present in organ	Reference
	(*E*)-β-guaiene (**60**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	(*Z*)-β-guaiene (**61**)	Leaf, inflorescence	Autran et al. (2009), Moraes et al. (2014)
	β-Gurjunene (**62**)	Leaf	Andrade et al. (2008)
	γ-Gurjunene (**63**)	Inflorescence	Autran et al. (2009)
	γ-Himachalene (**64**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	α-Humulene (**65**)	Leaf, stem, inflorescence	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986)
	Humulene epoxide II (**66**)	Leaf	Andrade et al. (2008)
	Isoledene (**67**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	(*Z*)-Isolongifolanone (**68**)	Stem	Autran et al. (2009)
	Ledol (**69**)	Leaf	Autran et al. (2009), Moraes et al. (2014)
	α-Muurolene (**70**)	Leaf	Andrade et al. (2008)
	γ-Muurolene (**71**)	Leaf, stem	Ramos et al. (1986)
	epi-α-Muurolol (**72**)	Leaf	Andrade et al. (2008)
	(*E*)-Nerolidol (**73**)	Leaf	Andrade et al. (2008), Sánchez et al. (2011)
	(*Z*)-Nerolidol (**74**)	Stem	Autran et al. (2009)
	Patchoulol (**75**)	Leaf, stem, inflorescence	Autran et al. (2009), Moraes et al. (2014)
	α-Selinene (**76**)	Leaf	Andrade et al. (2008)
	β-Selinene (**77**)	Leaf, stem	Andrade et al. (2008), Autran et al. (2009)
	7-*epi*-α-Selinene (**78**)	Leaf	Andrade et al. (2008)
	Selin-11-en-4α-ol (**79**)	Leaf	Andrade et al. (2008)
	Seychellene (**80**)	Stem	Autran et al. (2009)
	Spathulenol (**81**)	Leaf	Andrade et al. (2008)
	Valencene (**82**)	Inflorescence	Autran et al. (2009)
Phenylalkanoids	(*E*)-anethole (**83**)	Leaf, stem	Andrade et al. (2008), Sánchez et al. (2011), Vogler et al. (2006)
	(*Z*)-anethole (**84**)	Leaf	Andrade et al. (2008)
	p-Anisaldehyde (**85**)	Leaf, stem	Vogler et al. (2006)
	Anisyl ketone (**86**)	Leaf, stem	Vogler et al. (2006)
	Apiol (**87**)	Root	Santos et al. (1998)
	Asaricin (**88**)	Leaf	Andrade et al. (2008)
	(*E*)-asarone (**89**)	Leaf, stem, root, inflorescence	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014), Sánchez et al. (2011), Sánchez et al. (2011), Santos et al. (1998)
	(*Z*)-asarone (**90**)	Leaf, stem, inflorescence	Andrade et al. (2008), Autran et al. (2009), Moraes et al. (2014)
	γ-Asarone (**91**)	Leaf	Andrade et al. (2008)
	Croweacin (**92**)	Root	Andrade et al. (2008), de Oliveira Santos et al. (1997)
	Dillapiole (**93**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Sánchez et al. (2011)
	3,4-Dimethoxycinnamic acid (**94**)	Leaf	Sánchez et al. (2011)
	2,6-Dimethoxy-3,4-methylenedioxy-1-(2-propenyl)-benzene (**95**)	Root	Santos et al. (1998)
	Elemicin (**96**)	Leaf, stem	Autran et al. (2009), Moraes et al. (2014), Ramos et al. (1986), Sánchez et al. (2011)
	Estragole (**97**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Sánchez et al. (2011), Vogler et al. (2006)
	Exalatacin (**98**)	Leaf	Andrade et al. (2008)
	3-Farnesyl-4-hydroxybenzoic acid (**99**)	Leaf, stem	de Oliveira Chaves and de Oliveira Santos (2002), Maxwell and Rampersad (1988)
	3-Farnesyl-4-methoxybenzoic acid (**100**)	Leaf, stem	Maxwell and Rampersad (1988)
	2-Hydroxy-3,4-methylenedioxypropiophenone (**101**)	Leaf, stem	Andrade et al. (2008), de Diaz and Gottlieb (1979), Ramos et al. (1986)
	Isocroweacin (**102**)	Leaf	Sánchez et al. (2011)
	Isolelemicin (**103**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986)
	(*E*)-Isoosmorhizole (**104**)	Leaf	Andrade et al. (2008)
	Isosafrole (**105**)	Leaf	Sánchez et al. (2011)
	3,4-Methylenedioxy-1-(2E-octenyl)-benzene (marginatine, **106**)	Root	Santos et al. (1998)
	1-(3,4-Methylenedioxyphenyl)-propan-1-ol (marginatumol, **107**)	Leaf	Reigada et al. (2007)
	3,4-Methylenedioxypropiophenone (**108**)	Leaf, stem	Andrade et al. (2008), de Diaz and Gottlieb (1979), Ramos et al. (1986), Reigada et al. (2007)
	2-Methoxy-4,5-methylenedioxypropiophenone (**109**)	Root, leaf	Andrade et al. (2008), de Diaz and Gottlieb (1979), Oliveira Santos and Oliveira Chaves (2000), Reigada et al. (2007)
	Methyleugenol (**110**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Sánchez et al. (2011)
	Methyl 3-farnesyl-4-hydroxybenzoate (**111**)	Leaf, stem	Maxwell and Rampersad (1988)
	Methyl 3-farnesyl-4-methoxybenzoate (**112**)	Leaf, stem	Maxwell and Rampersad (1988)
	(*E*)-methyl isoeugenol (**113**)	Leaf, stem, inflorescence	Autran et al. (2009), Moraes et al. (2014)
	Methyl piperonate (**114**)	Leaf	Andrade et al. (2008)

Box 2 (*Continued*)

Class	Compound	Present in organ	Reference
	Myristicin (**115**)	Leaf, stem	Andrade et al. (2008), Ramos et al. (1986), Sánchez et al. (2011)
	Norepinephrine (**116**)	Leaf	D'Angelo et al. (1997)
	Nothosmyrnol (**117**)	Leaf	Sánchez et al. (2011)
	1-(1*E*-propenyl)-2,4,6-trimethoxybenzene (pipermargine, **118**)	Root	Santos et al. (1998)
	Piperonal (**119**)	Leaf, stem	de Diaz and Gottlieb (1979)
	1-(1-(*Z*)-propenyl)-2,4,6-trimethoxybenzene (**120**)	Fruit	de Oliveira Chaves and de Oliveira Santos (2002)
	Safrole (**121**)	Leaf, stem	Andrade et al. (2008), de Diaz and Gottlieb (1979), Ramos et al. (1986), Sánchez et al. (2011)
	2,4,5-Trimethoxypropiophenone (**122**)	Root	de Oliveira Santos and de Oliveira Chaves (1999b)
Alkaloids and amides	Cepharanone B (**123**)	Whole plant	de Oliveira Chaves et al. (2006)
	Cinnamoyl pirrolidide (**124**)	Stem	de Oliveira Chaves et al. (2003)
	(*E*,*E*)-*N*-isobutyl-2,4-octadienamide (**125**)	Root	de Oliveira Santos and de Oliveira Chaves (1999a)
	Piperolactam A (**126**)	Whole plant	de Oliveira Chaves et al. (2006)
Flavonoids	5,4′-Dihydroxy-7-methoxyflavanone (**127**)	Leaf	Reigada et al. (2007)
	5,7-Dihydroxy-4′-methoxyflavanone (**128**)	Leaf	Reigada et al. (2007)
	Marginatoside (**129**)	Leaf	Tillequin et al. (1978)
	Vitexin (**130**)	Leaf	Tillequin et al. (1978)
Others	Noradrenaline (**131**)	Leaf	D'Angelo et al. (1997)
	Stearic acid (**132**)	Leaf, stem	de Diaz and Gottlieb (1979)

from stem and flower being slightly more active than the EO from the leaf (Autran et al., 2009). A lower LC_{50} value of 8.3 μg/ml was reported for a leaf EO obtained from Paraiba, Brazil (Costa et al., 2010) whereas a LC_{50} value of 34 μg/ml was found for a leaf EO from a plant collected in the Rondonia state in Brazil (Santana et al., 2015). Moreover in the presence of the EO at 100 μg/ml, the gravid *A. aegypti* females reduced the number of eggs laid by one-third compared to the negative control (Autran et al., 2009). The effect of the *P. marginatum* EO on brine shrimp (*Artemia franciscana*) lethality and Vero cells cytotoxicity was found to be comparable in the concentration-response with a LC_{50} value of 22.4 μg/ml against the *A. franciscana* nauplii after 24 h of exposition (Olivero-Verbel et al., 2009), and an IC_{50} value of 30.3 μg/ml against the Vero cells (Tangarife-Castaño et al., 2014). In addition the EO also demonstrated antiparasitic and insecticidal properties, with 90% of the population of *Schistosoma mansoni* being inhibited with 5 mg of the EO (Frischkorn et al., 1978), and 90% of the population of the fire ant *Solenopsis saevissima* being inhibited with a concentration of 427–480 μg/ml (Souto et al., 2012). The EO of *P. marginatum* showed significant antioxidant activity with a DPPH IC_{50} value between 1.2 and 1.5 μg/ml while the control ascorbic acid showed a DPPH IC_{50} value of 1.0 μg/ml (Jaramillo-Colorado et al., 2015). Furthermore the EO demonstrated repellent activity of the red flour beetle *Tribolium castaneum* from a concentration of 0.01 μl/ml, and also a considerable anti-alimentary effect against the cotton moth *Spodoptera littoralis*, being non-phytotoxic against *Latucca sativa*, and thus suggesting a potential application as an natural agent to control beetles and moths in agricultural settings (Jaramillo-Colorado et al., 2015).

Both leaf and root from *P. marginatum* collected in Yutaje, Venezuela were extracted with ethanol and the ethanolic extracts were tested for cytotoxicity against a collection of cancer cell lines (Villasmil et al., 2006). The leaf extract was active against the human colon carcinoma line HT-29 with a GI_{50} of 55 μg/ml but inactive against the other cancer lines, whereas the root extract was found active against the human pancreatic carcinoma PANC-1 (GI_{50} 65 μg/ml), and moderately active against colon HT-29 (GI_{50} 298 μg/ml) and lung A549 (GI_{50} 240 μg/ml) carcinoma cell lines (Villasmil et al., 2006). A murine *in vivo* experiment was performed and the leaf extract showed a marked antitumoral effect decreasing by half the size of the tumors compared to the negative control. Interestingly the root extract was inactive suggesting that potential antitumoral compounds are present in the leaf but absent in the root, and thus these compounds could be easily differentiated by HPLC analysis of the extracts. The methanolic extract obtained from *P. marginatum* leaf collected in Pernambuco, Brazil, was examined for antifungal activity against the phytopathogenic fungi *Colletotrichum scovillei*, which causes anthracnose on bell peppers (Araújo et al., 2014). The methanolic extract displayed a dose-dependent inhibition of mycelial growth, achieving 50% inhibition with a concentration of 750 μg/ml. Although the methanolic extract was fractioned by column chromatography and a significantly active fraction was separated, the active antifungal compounds remains to be identified. Moreover the hydroalcoholic extract was screened for activity against *Leishmania infantum* amastigotes and showed an IC_{50} value of 25 μg/ml, while the positive control pentamidine showed an IC_{50} value of 2.43 μg/ml (Iwanaga et al., 2014).

P. marginatum has recurrently being employed in the traditional medicine as water decoction or infusion, and therefore D'Angelo and collaborators focused on the evaluation of *in vivo* pharmacological properties of the water extract (D'Angelo et al., 1997). There were no toxic effects observed on Wistar rats or albino mice when the water extract was administered orally up to 2 g/kg. However when administered intraperitoneally, a dose higher than 0.1 g/kg caused piloerection, quietness, lacrimation, muscle relaxation and dyspnea. At a intraperitoneal dose of 1.0 g/kg all animals died within 15 min (D'Angelo et al., 1997). The water extract also had a significant effect on blood pressure. The mean blood pressure of the control rats was 95.5 mmHg, while the intravenous administration of 0.1–0.5 mg/kg doses of *P. marginatum* water extract, clearly induced a dose-dependent increase to values ranging from 121.1 to 141.5 mmHg (D'Angelo et al., 1997). The hypertensive effect was also observed after oral administration of the water extract at 1 mg/kg. A dose-dependent increase of the rat mesenteric arterial pressure was also detected. In addition both in the vas deferens duct of the rat and the atria in the heart of the guinea pig, the frequency of contractions increased in a dose-dependent manner with the administration of the water extract. The water extract when administered orally at 0.5 and 1.0 mg/kg displayed analgesia in the writhing test in mice and a significant reduction on the edema (inflammation) of the rat paw induced by carrageenan. There was no effect of the *P. marginatum* water extract on leukocyte

Box 3
Biological and pharmacological activities of *Piper marginatum*.

Extract or compound	Biological activity	Assay	Potency	References
Leaf EO	Antibacterial	*In vitro* against two pathogenic strains of *Escherichia coli*	MIC (STEC0157) = 700 μg/ml MIC (EPEC0312) = 900 μg/ml	Duarte et al. (2007)
		In vitro against *Xanthomonas albilineans*	MIC = 120 μg/ml	Sánchez et al. (2012)
	Antifungal	*In vitro* against *Fusarium oxysporum*	Inhibition diameter = 22.5 mm, Control diameter = 69.9 mm	dos Santos et al. (2011)
		In vitro against *Alternaria solanii*	Inhibition % = 57 with 10 μl of EO	Duarte et al. (2013)
	Larvicidal	*In vitro* against *Aedes aegypti* larvae	LC_{50} = 8.3 μg/ml Control temefos LC_{50} = 0.3 μg/ml	Costa et al. (2010)
			LC_{50} = 34 μg/ml LC_{90} = 85 μg/ml	Santana et al. (2015)
EO	Antifungal	*In vitro* against *Candida albicans*	MIC > 2.0 mg/ml	Duarte et al. (2005)
	Antifungal and cytotoxicity	*In vitro* activity against *Fusarium oxysporum*, *Trichophyton rubrum* and *Trichophyton mentagrophytes* and cytotoxicity against Vero cell line	*F. oxysporum* MIC > 500 μg/ml *T. rubrum* MIC = 500 μg/ml *T. mentagrophytes* MIC = 250 μg/ml. IC_{50} = 30.3 μg/ml against Vero cell line	Tangarife-Castaño et al. (2014)
	Antioxidant, repellent, anti-alimentary and phytotoxic	*In vitro* DPPH antioxidant, *Tribolium castaneum* repellent, *Spodoptera littoralis*, antialimentary, and *Latucca sativa* and *Lolium perenne* phytotoxicity activities	DPPH inhibition with IC_{50} = 1.2–1.5 μg/ml, while the control ascorbic acid showed IC_{50} = 1.0 μg/ml. EO repellent of >50% *T. castaneum* from 0.01 μl/ml EO anti-alimentary to *S. littoralis* with 64–80% effect with 100 $\mu g/cm^2$ EO (at unknown concentration) inhibited root growth of *L. perenne* by 54–62%, but increased root growth of *L. sativa* by 119–170%	Jaramillo-Colorado et al. (2015)
	Brine shrimp lethality	*In vitro* against *Artemia franciscana* cysts	LC_{50} = 22.38 μg/ml (at 24 h) LC_{50} = 12.64 μg/ml (at 48 h)	Olivero-Verbel et al. (2009)
	Cercaricidal	*In vitro* against *Schistosoma mansoni*	At 10 mg, 96% of cercariae died At 5 mg, 90% of cercariae died At 1 mg, 24% of cercariae died	Frischkorn et al. (1978)
	Larvicidal	*In vitro* against *Aedes aegypti* larvae	Leaf EO LC_{50} = 23.8 μg/ml Stem EO LC_{50} = 19.9 μg/ml Flower EO LC_{50} = 19.9 μg/ml	Autran et al. (2009)
	Insecticidal	*In vitro* against the workers of the fire ant *Solenopsis saevissima* (Smith)	LC_{50} = 122–167 μg/ml LC_{90} = 427–480 μg/ml	Souto et al. (2012)
	Oviposition	*In vitro* on gravid *Aedes aegypti* females and counting the number of eggs laid	% eggs laid (leaf) = 33% % eggs laid (stem) = 32% % eggs laid (flower) = 35% At 100 μg/ml with respect to the negative control	Autran et al. (2009)
Ethanolic extract	Cytotoxicity	*In vitro* against murine melanoma B16/BL6, human colon carcinoma HT-29, human lung carcinoma A549, human cervical carcinoma HeLa, and human pancreatic carcinoma PANC-1	Leaf: B16/BL6 GI_{50} > 300 μg/ml HT-29 GI_{50} = 55 μg/ml A549 GI_{50} > 300 μg/ml HeLa GI_{50} > 300 μg/ml PANC-1 GI_{50} > 300 μg/ml Root: B16/BL6 GI_{50} > 300 μg/ml HT-29 GI_{50} = 298 μg/ml A549 GI_{50} = 240 μg/ml HeLa GI_{50} > 300 μg/ml PANC-1 GI_{50} = 65 μg/ml	Villasmil et al. (2006)
	Antitumoral	*In vivo* murine tumor induction assay	The leaf extract (and not the root extract) of *P. marginatum* showed antitumoral activity	Villasmil et al. (2006)
Methanolic extract	Antifungal	*In vitro* against *Colletotrichum scovillei*	The percentage of inhibition of mycelial growth (PIC) was 50% with a concentration of 750 μg/ml, and reached 70% at 1.5 mg/ml	Araújo et al. (2014)
Hydro-alcoholic extract	Anti-leishmanial	*In vitro* against *Leishmania infantum* amastigotes	IC_{50} = 25 μg/ml The positive control pentamidine showed IC_{50} = 2.43 μg/ml	Iwanaga et al. (2014)

Box 3 (*Continued*)

Extract or compound	Biological activity	Assay	Potency	References
Water extract	Toxicity	*In vivo* on Wistar adult rat and albino mice	LD_{100} = 1 g/kg (intraperitoneal) LD > 2 g/kg (orally)	D'Angelo et al. (1997)
	Blood pressure	*In vivo* on rat	Dose-dependent hypertension was observed with intravenous and oral administrations	D'Angelo et al. (1997)
	Vas deferens contractility	*In vivo* on rat	Dose-dependent contractions with EC = 38.02 μg/ml	D'Angelo et al. (1997)
	Atria contractility	*In vivo* on guinea pig	Dose-dependent contractions with doses between 2.5 and 10 μg/ml	D'Angelo et al. (1997)
	Perfused mesenteric bed pressure	*In vivo* on rat	Dose-dependent increase of the perfusion pressure of mesenteric arteria with EC = 159.6 μg	D'Angelo et al. (1997)
	Analgesia	*In vivo* on mice	A reduction of twist movements was observed in treated animals with 0.5 and 1.0 mg/kg oral doses	D'Angelo et al. (1997)
	Anti-inflammatory of paw edema	*In vivo* on rat	Dose-dependent reduction of swelling with 0.5 and 1.0 mg/kg oral doses	D'Angelo et al. (1997)
	Pleural leukocyte count	*In vivo* on rat	No effect on exudate volume and leukocyte count with 0.5 and 1.0 mg/kg oral doses	D'Angelo et al. (1997)
Purified flavonoids	Antifungal	*In vitro* autobiography against *Cladosporus cladosporioides* and *Cladosporus sphaerospernum*	Amount required to inhibit both *C. cladosporioides* and *C. sphaerospernum*: (**107**) – 10.0 μg (**108**) – 5.0 μg (**109**) – 5.0 μg (**127**) – 1.0 μg (**128**) – 1.0 μg	Reigada et al. (2007)

counts in the pleurisy induced by carrageenin, suggesting that the anti-inflammatory effect is related to a vasoconstriction action of the water extract of *P. marginatum*, and not a specific anti-inflammatory action (D'Angelo et al., 1997).

Among all the identified secondary metabolites present in *P. marginatum*, only five have been tested for a biological activity and these are three arylpropanoids 1-(3,4-methylenedioxyphenyl)-propan-1-ol (marginatumol, **107**), 3,4-methylenedioxypropiophenone (**108**), 2-methoxy-4,5-methylenedioxypropiophenone (**109**), and the two flavanones 5,4′-dihydroxy-7-methoxyflavanone (**127**) and 5,7-dihydroxy-4′-methoxyflavanone (**128**). A bioautographic method was employed to evaluate their antifungal effect against *Cladosporus cladosporioides* and *Cladosporus sphaerospernum* and the most active compounds were the two flavanones (**127**) and (**128**), which inhibited both microorganisms with an amount as little as 1 μg (Reigada et al., 2007). The two propiophenones (**108**) and (**109**) inhibited the growth of the fungi with 5 μg, whereas the alcohol marginatumol, (**107**) required 10 μg to inhibit the fungi.

Conclusion

The species *P. marginatum*, widely used in the traditional medicine of the Caribbean region, primarily to treat gastrointestinal problems but also employed as analgesic, hemostatic and to cure insect bites, contains a variable mixture of terpenoids, phenylalkanoids, amides and flavonoids. Some of these compounds, including anethole, estragole, isoeugenol methyl ether, 3-farnesyl-4-hydroxybenzoic and 3-farnesyl-4-methoxybenzoic acids, marginatoside and vitexin, are not present in other *Piper* species, and are thus chemotaxonomic markers for *P. marginatum*. The high variability of chemotypes observed within *P. marginatum sensu lato* may reflect upon speciation events, or other factors which remains to be fully investigated. The distinctiveness of the chemical composition translate into a range of biological and pharmacological applications, which according to the reported potency, the larvicidal effect against *A. aegypti*, the antifungal activity against phytopathogenic fungi and the hemostatic and antitumoral potential, are worth highlighting for future research.

Authors' contributions

JB and JDG searched the literature. JB collected data in tables. JDG organized the information, prepared the figures and wrote the paper.

Conflicts of interest

The authors declare no conflicts of interest.

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