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Traditional Uses, Chemical Profile and Biological Activities of *Piper hispidum* Sw.: a Review

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Abstract: *Piper hispidum* Sw. (Piperaceae) (syn. *Piper hispidinervum*) is a medicinal shrub distributed in Central and South America, widely used as an astringent, diuretic, stimulant for unblocking the liver and stopping hemorrhages. The plant has great interest among researchers due to the production of essential oil and important raw material for the chemical industry, which has a high demand for cosmetic, insecticide, and pesticide industries. In this review, traditional uses, phytochemicals, and biological activities of *P. hispidum* are comprehensively and systematically summarized through searching scientific databases, including Science Direct, PubMed, Google Scholar, Scopus, and Web of Science. Phytochemical studies revealed the presence of amides, benzoic acids, flavonoids, phenylpropanoids, butenolides, phenol, and essential oils; hence it has several activities, such as antioxidant, antibacterial, α-amylase, insecticidal, schistosomicidal, leishmanial, larvicidal, antiplasmodial, cytotoxicity, estrogenic and serotonergic properties. This review is expected to draw the attention of medical professionals and the general public towards *P. hispidum* as well as to open the door for detailed research in the future.

Keywords: *Piper hispidum*; *Piper hispidinervum*; amide; benzoic acid; essential oil; leishmanial.

1. Introduction

The Piperaceae family belongs to the Nymphaeiflorae superorder, of the Piperales order, and includes approximately 2500 species distributed in five genera (*Piper*, *Peperomia*, *Zippelia*, *Manekia*, and *Verhuellia*). Piperaceae can be found in herbs, vines, shrubs, and trees more rarely [1-3]. *Piper* is the most economically and ecologically important genus of the Piperaceae family. It is represented by herbs, shrubs, and trees and is widely distributed in the world's tropical and subtropical regions. It consists of a wide variety of species of high economic value, as they are used as food aromas, perfumes, fish venom, insecticides, as well as in the treatment of gynecological and gastrointestinal disturbances, depression, anxiety, pain, and inflammations, as well as bacterial and fungal infections [4-6]. Moreover, *Piper* species are used to treat diseases, including fever, jaundice, rheumatism, and neuralgia, in various countries' folk medicine [7]. Chemical studies have shown that *Piper* has many classes of compounds, such as amides, alkaloids, flavonoids, lignans, neolignans, aristolactams, terpenes, steroids, and phenylpropanoids [8].

Piper hispidum Sw. is a herbaceous plant that grows in tropical and subtropical regions of the world, is widely distributed over a large geographic region, and can be found in Central America, the Andes, and South America. It is one of the plants that is abundantly used because of its medicinal properties [9,10]. *Piper hispidinervum* C.DC. is a synonym of *Piper hispidum* Sw., known as "*pimenta-longa*" in Brazil. This species resembles *Piper aduncum* L. to some extent but differs in its scarcely scabrous leaves, glabrous stem, and short peduncle. It is distributed throughout South America and is especially prominent in Acre's state in Brazil, and may extend into Amazonas [11].

The current review aims to provide a concise summary of the available information of *P. hispidum* (including *P. hispidinervum*), particularly concerning its traditional uses, phytochemistry, and biological activities. The pharmacological activities and chemical constituents of P. hispidum are also discussed by highlighting its pharmacological potential and identifying this plant as a natural source for potential drug compounds. This review was conducted through searches using Science Direct, PubMed, Google Scholar, Scopus, and Web of Science. The keywords used were "*Piper hispidum*", "*Piper hispidinervum*", "*Piper*", "phytochemistry", "biological activity", and "essential oils" articles over the period from the beginning of the database until May 2020. As a second search strategy, we included studies obtained by a manual search of the included studies' reference lists.

2. Plant Profile

The Plant List includes 88 synonym plant names of *P. hispidum* [12]. It is commonly known as *platanillo-de-cuba* and *bayuyo* (Cuba), *cordoncillo* (Mexico), *jaborandi*, *matico* or *aperta-joão*, and *falso-jaborandi* (Brazil) [13]. *P. hispidum* is a shrub with cylindrical and green stem, which has alternate leaves. The main anatomical characteristics that can be used in its identification are root with sclereids on cortical parenchyma, stem cortex with discontinuous strands of angular collenchyma, and vascular tissue constituted by two discontinuous circles of collateral vascular bundles. The leaf is dorsiventral and hypostomatic with tetracytic stomata. The hypodermis is discontinuous in the adaxial face, loose in the abaxial one, and presents a variable number of layers. Uniseriate epidermis and oil idioblasts occur in all organs [14].

3. Traditional Uses

Previous research has reported the use of *P. hispidum* to ease the pain of childbirth, anemia, and rheumatism in Nicaragua [15]. In addition, the inflorescence is applied topically for muscle aches [16]. The Q'eqchi Maya tribe in Guatemala used this plant to treat female reproductive disorders, including amenorrhea, dysmenorrhea, and menopause [17]. The plant's leaves are also traditionally used by the Chayahuitas, an Amazonian Peruvian ethnic group in Peru, to heal wounds and treat symptoms of cutaneous leishmaniasis [18]. It has also been used as an insecticide, astringent, diuretic, stimulant, liver treatment, and for stopping hemorrhages [19]. In Colombia, the tea of the decoction of *P. hispidum* leaves is useful for the treatment of malaria [20], while in Jamaica, the infusion of leaves in combination with *P. aduncum* is used to treat stomach pains and colds [21].

A leaf infusion is applied to kill head lice in Ecuador, while in Panama, it is used to treat conjunctivitis and diarrhea [22]. Meanwhile, the Totonacs ethnic group from Mexico used to treat mumps and tonsillitis and prevent tooth decay [23]. In South and Central America (particularly Brazil, Colombia, Ecuador, Guatemala, Honduras, Mexico, Panama, and Peru), it is popularly used for snakebites, insect bites, skin cleansing, head lice, amygdalitis, mouth sores, and teeth whitening agent [24]. Meanwhile, *P. hispidinervum* oil is an important raw source of safrole, a chemical used to synthesize piperonyl butoxide (PBO), a vital ingredient of pyrethroid insecticides [25].

4. Phytochemistry

Up to now, 43 compounds have been reported from *P. hispidum* including eleven amides (**1**-**11**) [26-30], seven benzoic acids (**12**-**18**) [29,31], sixteen flavonoids (**19**-**34**) [30-35], five phenylpropanoids (**35**-**39**) [29,31,34], butenolides (**40**-**42**) [36], and one phenol (**43**) [33]. Amides are the predominant secondary metabolite constituents in *P. hispidum*. Their structures, names, plant part, and references are collected in Table 1 and Figure 1.

4.1. Amides.

Eleven amides (**1**-**11**) were successfully identified from the roots of *P. hispidum*. Recently, Lima *et al.* [26] reported the isolation of four amides (**1**-**4**), obtained by supercritical carbon dioxide extraction procedure. Amides (**1**) and (**2**) were found as a mixture, as determined by GC-MS. Another study, Alecio *et al.* [27] was successfully identified a new pyrrolidine amide, *N*-[7-(3',4'-methylenedioxyphenyl)-2(*Z*),4(*Z*)-heptadienoyl]pyrrolidine (**5**), along with two known amides, identified as *N*-[5-(3',4'-methylenedioxyphenyl)-2(*E*)-pentadienoyl]-pyrrolidine (**6**) and *N*-[2-(3',4'-methylenedioxy-6'-methoxyphenyl)-2(Z)-propenoyl]-pyrrolidine (**7**) from the dichloromethane extract of the dried leaves part. Besides, Friedrich *et al.* [29] and Ruiz *et al.* [30] managed to isolate *N*-*trans*-feruloyltyramine (**8**) and *N*-2-(3',4',5'-trimethoxyphenyl)ethyl-2-hydroxybenzamide (**11**) from the stems and leaves parts of *P. hispidum*, respectively. Meanwhile, Navickiene *et al.* [28] were successfully characterized two amides, known as (3*Z*,5*Z*)-*N*-isobutyl-8-(3',4'-methylenedioxy-phenyl)-heptadienamide (**9**) and *N*-[3-(6'-methoxy-3',4'-methylenedioxyphenyl)-2(*Z*)-propenoyl]pyrrolidine (**10**).

4.2. Benzoic acids.

Seven benzoic acids (**12**-**18**) have been reported phytochemically from *P. hispidum* [29,31]. Friedrich *et al.* [29] were successfully isolated and characterized three new 4-hydroxy-benzoic acid derivatives, 4-methoxy-3,5-bis-(3-hydroxy-3-methyl-1-butenyl)benzoate (**12**), 3-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran-5-carboxylic acid methyl ester (**13**), and 3-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran-5-carboxylic acid (**14**), along with nervogenic acid (**15**), nervogenic acid methyl ether (**16**), 2,2-dimethyl-8-(3-methyl-2-butenyl)-2*H*-chromene-6-carboxylic acid (**17**), and 4-hydroxy-3-(3-methyl-2-butenyl)benzoate (**18**) from the methanolic extract of the stems of *P. hispidum*.

4.3. Flavonoids.

Fourteen flavonoids (**19**-**34**) have been isolated phytochemically from *P. hispidum* [30-34]. It comprises six flavanones (**19**-**24**) and nine chalcones (**25**-**34**). Erika *et al.* [32] were successfully characterized two known flavonoids, identified as 5-hydroxy-7-methoxyflavanone (**20**) and 5-hydroxy-4',7-dimethoxyflavanone (**21**) from the ethanolic extract of the inflorescences of *P. hispidum.* In another study, Vieira *et al.* [33] were reported 6-hydroxy-5,7-dimethoxyflavanones (**22**), 8-hydroxy-5,7-dimethoxyflavanones (**23**), and

5,7,8-trimethoxyflavanones (**24**) from the Brazillian leaves extract. In the case of chalcones, Costa *et al.* [35] managed to isolate three compounds, known as 2'-hydroxy-4,4',6'-trimethoxychalcone (**31**), 2'-hydroxy-3,4,4',6'-tetramethoxychalcone (**32**), and 2',3-dihydroxy-4,4',6'-trimethoxychalcone (**33**) from the same part. In the meantime, 2',4',6-trimethoxychalcone (**25**), 2',6'-dihydroxy-4'-methoxychalcone (**27**), and 2'-hydroxy-3',4',6'-trimethoxychalcone (**28**) have been isolated from the inflorescences, fruits and leaves part of *P. hispidum*, respectively [30-33].

Table 1. Phytochemicals identified from *P. hispidum* and bioactivities.

No	Compounds	Part	Bioactivities	Ref
	AMIDES			
1	(*Z*)-3-(6-methoxybenzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)prop-2-en-1-one	Leaves		[24]
2	(*E*)-3-(6-methoxybenzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)prop-2-en-1-one	Leaves	**Cytotoxicity:** Inhibition of 9.19% (HepG2) and 62.11% (HL-60)	[24]
3	(2*Z*,4*E*)-7-(benzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one	Leaves		[24]
4	(2*E*,4*Z*)-7-(benzo[d][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one	Leaves		[24]
5	*N*-[7-(3',4'-methylenedioxyphenyl)-2(*Z*),4(*Z*)-heptadienoyl]pyrrolidine	Leaves	**Antifungal:** MIC value 8.0 μg against *Cladosporium sphaerospermum*	[25]
6	*N*-[5-(3',4'-methylenedioxyphenyl)-2(*E*)-pentadienoyl] pyrrolidine	Stems	**Antifungal:** MIC value 5.0 μg/mL against *Cladosporium sphaerospermum*	[26]
		Leaves		[25]
7	*N*-[2-(3',4'-methylenedioxy-6'-methoxyphenyl)-2(Z)-propenoyl]-pyrrolidine	Leaves		[25]
8	*N*-trans-feruloyltyramine	Stems		[27]
9	(3*Z*,5*Z*)-*N*-isobutyl-8-(3',4'-methylenedioxy-phenyl)-heptadienamide	Stems	**Antifungal:** MIC value 5.0 μg/mL against *Cladosporium sphaerospermum*	[26]
10	*N*-[3-(6'-methoxy-3',4'-methylenedioxyphenyl)-2(*Z*)-propenoyl]pyrrolidine	Stems	**Antifungal:** MIC value 5.0 μg/mL against *Cladosporium sphaerospermum*	[26]
11	*N*-2-(3',4',5'-trimethoxyphenyl)ethyl-2-hydroxybenzamide	Leaves		[28]
	BENZOIC ACIDS			
12	4-Methoxy-3,5-bis-(3-hydroxy-3-methyl-1-butenyl)benzoate	Stems		[27]
13	3-Hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran-5-carboxylic acid methyl ester	Stems		[27]
14	3-Hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofuran-5-carboxylic acid	Stems		[27]
15	Nervogenic acid	Stems		[27]
16	Nervogenic acid methyl ether	Stems		[27]
		Fruits		[29]
17	2,2-Dimethyl-8-(3-methyl-2-butenyl)-2H-chromene-6-carboxylic acid	Stems		[27]
18	4-Hydroxy-3-(3-methyl-2-butenyl)benzoate	Stems		[27]
	FLAVONOIDS			
19	5,7-Dihydroxyflavanone	Leaves		[28]
20	5-Hydroxy-7-methoxyflavanone	Fruits		[29]
		Inflorescences		[30]
21	5-Hydroxy-4',7-dimethoxyflavanone	Inflorescences		[30]
22	6-Hydroxy-5,7-dimethoxyflavanones	Leaves		[31]
23	8-Hydroxy-5,7-dimethoxyflavanones	Leaves		[31]
24	5,7,8-Trimethoxyflavanones	Leaves		[31]
25	2',4',6-Trimethoxychalcone	Inflorescences		[30]
26	2',4',6-Trihydroxychalcone	Leaves		[32]
27	2',6'-Dihydroxy-4'-methoxychalcone	Fruits		[29]
28	2'-Hydroxy-3',4',6'-trimethoxychalcone	Leaves	**Antileishmanial:** IC_{50} values of 0.8 μM against *Leishmania amazonensis* **Cytotoxicity:** IC_{50} values of 1.6 μM against peritoneal macrophages	[28]

No	Compounds	Part	Bioactivities	Ref
		Branch		[31]
29	2',4'-Dihydroxy-6'-methoxychalcone	Leaves	**Antileishmanial:** IC_{50} values of 8.0 μM against *Leishmania amazonensis* **Cytotoxicity:** IC_{50} values of 18.2 μM against peritoneal macrophages	[28]
30	2',3'-Dihydroxy-4',6'-dimethoxychalcones	Branch		[31]
31	2'-Hydroxy-4,4',6'-trimethoxychalcone	Leaves	**Antimicrobial:** MIC value of 125 and 250 μg/mL against *S. aureus* and *C. albicans*	[33]
32	2'-Hydroxy-3,4,4',6'-tetramethoxychalcone	Leaves	**Antimicrobial:** MIC value of 250 and 500 μg/mL against *S. aureus* and *C. albicans*	[33]
33	2',3-Dihydroxy-4,4',6'-trimethoxychalcone	Leaves	**Antimicrobial:** MIC value of 125 and 250 μg/mL against *S. aureus* and *C. albicans*	[33]
34	2',4,6'-Trihydroxy-4'-methoxychalcone	Leaves	**Antiplasmodial:** IC_{50} values of 16.9 μg/mL (poW) and 10.4 μg/mL (Dd2) active against both a chloroquine-sensitive and a resistant strain of *Plasmodium falciparum*	[32]
	PHENYLPROPANOIDS			
35	ω-Hydroxyisodillapiole	Stems	**Cytotoxicity:** IC_{50} values of 31.8 μg/mL against human bladder carcinoma cell line ECV-304	[27]
36	Dillapional	Stems	**Cytotoxicity:** IC_{50} values of 31.7 μg/mL against human bladder carcinoma cell line ECV-304	[27]
37	Dillapiole aldehyde	Stems	**Cytotoxicity:** IC_{50} values of 31.1 μg/mL against human bladder carcinoma cell line ECV-304	[27]
38	Dillapiole	Leaves		[32]
39	1-Allyl-2,3-(methylenedioxy)-4,5-dimethoxy-benzene	Fruits		[29]
	BUTENOLIDES			
40	9,10-Methylenedioxy-5,6-*Z*-fadyenolide	Leaves	**Estrogenic and serotonergic:** Bound to the serotonin receptor 5-HT7 with IC50 values of 16.1 and 8.3 μM, respectively, and using GTP shift assays, it was found to be a partial agonist of the 5-HT7 receptor	[34]
41	5,6-*Z*-Fadyenolide	Leaves		[34]
42	Piperolide	Leaves		[34]
	PHENOL			
43	4-(5'*E*-*n*-hexadecenyl)-phenol	Leaves		[31]

4.4. Phenylpropanoids.

Friedrich *et al.* [29] managed to isolate three phenylpropanoids, identified as ω-hydroxyisodillapiole (**34**), dillapional (**35**), and dillapiole aldehyde (**36**), from the part of the stem. Meanwhile, a long time ago, Burke and Nair, [31] reported the isolation of 1-allyl-2,3-(methylenedioxy)-4,5-dimethoxy-benzene (**39**) from the fruits of *P. hispidum.*

4.5. Butenolides.

Three butenolides, including one new compound, 9,10-methylenedioxy-5,6-*Z*-fadyenolide (**40**) were isolated from the leaves of *P. hispidum* collected from Guatemala [36]. Other butenolides were 5,6-*Z*-fadyenolide (**41**) and piperolide (**42**).

4.6. Phenol.

4-(5'*E*-n-hexadecenyl)-phenol (**43**) was the only phenol found in the leaves of *P. hispidum*, as reported by Vieira *et al.* [33].

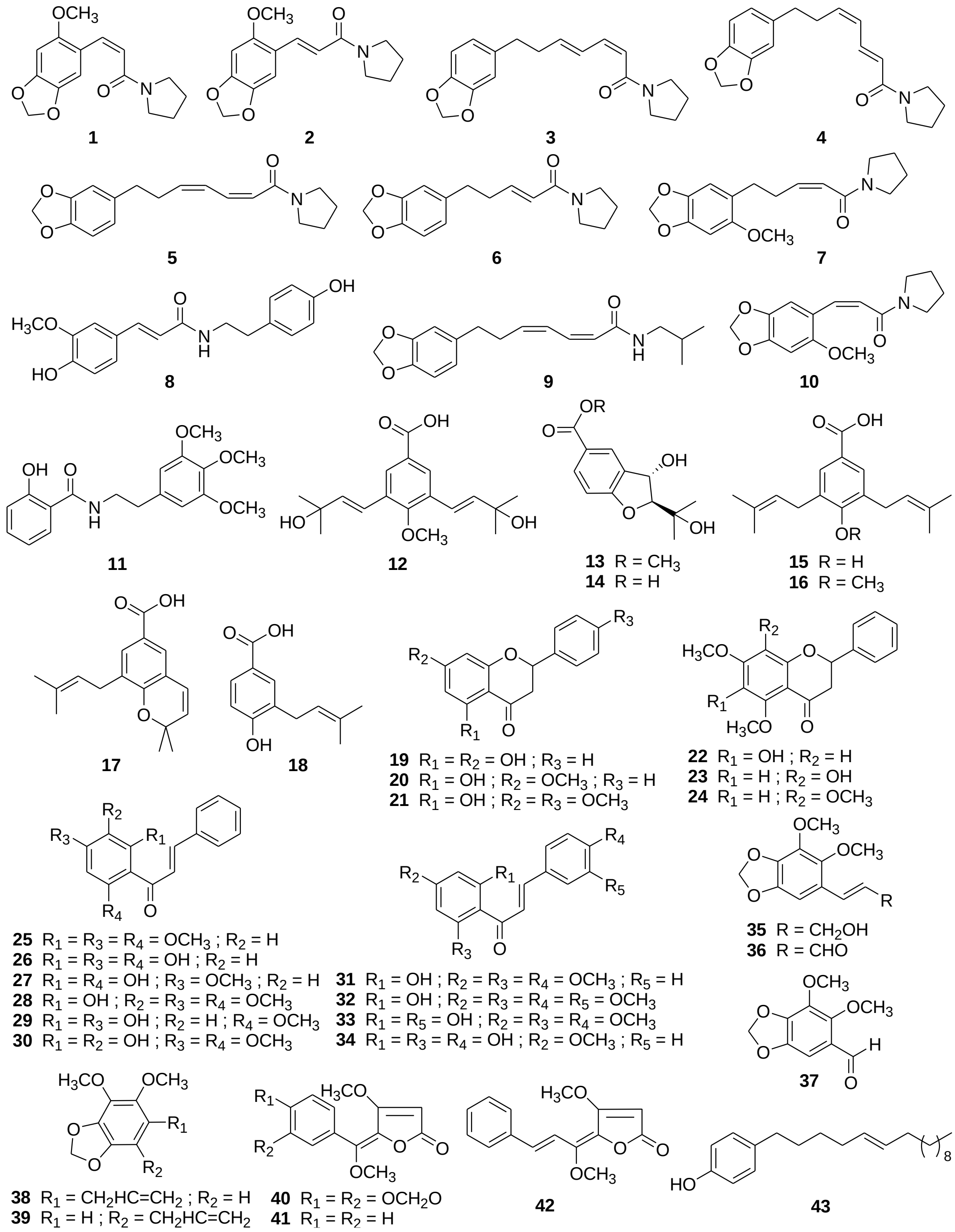

Figure 1. Chemical structures of isolated compounds from *P. hispidum.*

4.7. Essential oils.

Essential oils are complex mixtures of volatile compounds, mainly terpenes and oxygenated aromatic and aliphatic compounds, such as phenols, alcohols, aldehydes, ketones, esters, lactones, coumarins, ethers, and oxides, biosynthesized and accumulated in many plants. These naturally occurring mixtures of volatile compounds have been gaining increasing interest because of their wide range of applications in pharmaceutical, sanitary, cosmetics, perfume, food, and agricultural industries. Several significant biological activities are attributed to essential oils, such as allelopathic, antibacterial, antifungal, antioxidant, anti-inflammatory, and anticancer activities [37-48].

The chemical compositions of *P. hispidum* essential oils have been reported from various origins including Brazil [49-56], Colombia [57-59], Cuba [60], France [61], Guatemala

[62], Panama [63], and Venezuela [64]. Most of the essential oils successfully identified monoterpenes as the major components, which are γ-terpinene, β-pinene, α-pinene, limonene, δ-3-carene, and α-copaene. In addition, sesquiterpenes were identified as the most dominant component, which are β-caryophyllene, γ-cadinene, curzerene, and germacrene D. Besides, oxygenated sesquiterpenes characterized as *trans*-nerolidol, β-eudesmol, and spathulenol have been reported from *P. hispidum* essential oils collected from Colombia, Cuba, and Guatemala, respectively. *P. hispidum* essential oils also presented a phenylpropanoid, dillapiole. Its richness in the leaves and roots part was collected from Brazil and Panama. Table 2 summarizes the data on the major components and biological activities of *P. hispidum* (and *P. hispidinervum*) [65-68] essential oils.

Table 2. Components identified from *P. hispidum* and *P. hispidinervum* essential oils and bioactivities.

Country	Parts	Total No	Total %	Major components (%)	Bioactivities	Ref
Brazil	Leaves	32	99.7	γ-Terpinene (30.9%), α-terpinene (14.4%), *p*-cymene (12.1%), α-selinene (9.0%), β-selinene (8.1%)	**Antifugal:** MIC and MFC values of 312.5 and >1250 μg/mL against *Rhizopus oryzae*	[15]
Brazil	Leaves	33	92.8	Khusimene (12.1%), β-pinene (12.0%), γ-cadinene (13.2%), ledol (8.8%)	**Toxicity:** LC_{50} value of 404.8 μg/mL against *Artemsia salina*	[49]
Brazil	Aerial parts	61	88.4	β-Caryophyllene (10.5%), α-humulene (9.5%), α-copaene (7.3%), limonene (6.9%), caryophyllene oxide (5.9%)	**Cytotoxicity:** IC_{50} value of >25 μg/mL against HCT-116, SKMEL19, and ACP03 cell lines **Antifungal:** Detection limit (DL) of 0.1 μg/mL (*Cladosporium cladosporioides*) and 1.0 μg/mL (*Cladosporium sphareospermum*) **Antioxidant:** Inhibition of 26.4% (DPPH); TEAC (303.1 mg ET/mL) **AChE:** Detection limit (DL) of 0.01 μg/mL	[50]
Brazil	Roots	8	99.9	Dilapiole (57.5%), elemicin (24.5%), apiol (10.2%)		[20]
Brazil	Leaves	11	97.2	γ-Cadinene (25.13%), camphene (15.61%), α-guaiene (11.47%), γ-elemene (10.88%)		[51]
Brazil	Leaves	38	99.0	γ-Terpinene (27.3%), p-cymene (14.0%), α-terpinene (12.0%), α-selinene (8.4%), β-selinene (7.5%), terpinolene (6.5%)	**Antimicrobial:** MIC value of 937.5 μg/mL against *Aeromonas hydrophila*	[52]
Brazil	Leaves	36	75.2	β-pinene (9.76%), α-pinene (6.90%), (*E*)-nerolidol (6.30%), γ-cadinene (5.3%), δ-cadinene (5.0%)		[53]
Brazil	Fruits	99	70.0	limonene (16.3%), β-pinene (14.5%), α-pinene (13.5%), linalool (9.6%), α-terpineol (8.5%) , 1,8-cineol (5.1%)		[54]
Brazil	Ripe fruits	47	98.1	α-Copaene (36.2%), β-pinene (7.5%), α-pinene (7.1%), (*E*)-nerolidol (7.0%)		[55]
	Unripe fruits	44	97.8	α-copaene (28.7%), α-pinene (13.9%), β-pinene (13.3%)		
Brazil	Fresh leaves	17	95.1	Germacrene D (33.9%), δ-3-carene (17.4%), (*E*)-caryophyllene (13.8%), bicyclogermacrene (7.1%)		[56]
	dried leaves	21	94.1	Germacrene D (31.0%), δ-3-carene (19.1%), (*E*)-caryophyllene (14.9%), bicyclogermacrene (6.2%)	**Cytotoxicity:** Inhibition of 62.8% (HepG2) and 70.2% (HL-60) **Larvicidal:** LC_{50} value of 141.9 μg/mL against *Aedes aegypti*	

Country	Parts	Total		Major components (%)	Bioactivities	Ref
		No	%			
	Stems	17	85.4	Germacrene D (18.8%), (*E*)-caryophyllene (14.2%), δ-cadinene (10.6%), bicyclogermacrene (9.3%), α-ylangeno (6.5%), α-muurolol (6.2%)	**Cytotoxicity:** Inhibition of 47.7% (HepG2) and 16.3% (HL-60)	
Colombia	Aerial parts	44	99.4	*trans*-Nerolidol (23.6%), caryophyllene oxide (5.4%), β-elemene (5.1%), *trans*-β-caryophyllene (5.1%)	**Antifungal:** MIC values of 99 μg/mL (*T. rubrum*) and 125 μg/mL (*T. mentagrophytes*) **Cytotoxicity:** IC_{50} value of 51.7 μg/mL against Vero cell line	[57] [58]
Colombia	Leaves	17	87.5	δ-3-Carene (9.6%), p-cymene (10.9%), limonene (17.2%), elemol (14.1), γ-elemene (7.3%), β-eudesmol (5.7%)	**Antifeedant:** EC_{50} value of 48.0 μg/mL against *Spodoptera littoralis* **Phytotoxic:** Percentage control of 94.5% against *Lolium perenne*	[59]
Cuba	Leaves	25	93.5	β-eudesmol (17.5%), *trans*-6-vinyl-4,5,6,7-tetrahydro-3,6-dimethyl-5-isopropenylbenzofuran (12.9%), γ-eudesmol (9.3%), α-eudesmol (8.1%), elemol (7.6%)		[60]
France	Leaves	64	90.5	Curzerene (15.7%), germacrene B (10.9%), α-selinene (10.5%), β-selinene (7.6%)	**Antidermatophytic:** MIC value of 62 μg/mL against *Trichophyton mentagrophytes* **Antileishmanial:** IC_{50} value of 3.4 μg/mL against *Leishmania amazonensis* **Cytotoxicity:** TD_{50} value of 35.5 μg/mL against BALB/c mice peritoneal macrophages	[61]
Guatemala	Leaves	23	74.9	Spathulenol (8.7%), β-caryophyllene (6.9%), (*E*)-nerolidol (6.8%), germacrene D (6.0%), caryophyllene oxide (5.9%)		[62]
Panama	Leaves	43	95.1	Dillapiole (57.7%), piperitone (10.0%)	**Larvicidal:** LC_{100} value of 250 μg/mL against *Aedes aegypti*	[63]
Venezuela	Leaves	34	95.2	α-pinene (15.3 %), β-pinene (14.8 %), β-elemene (8.1 %), caryophyllene oxide (7.8 %), δ-3-carene (6.9 %)	**Antimicrobial:** MBC values of 12.5 μg/mL against *S. aureus, S. epidermides, S. saprophyticus, B. cereus, B. subtilis* **Cytotoxicity:** IC_{50} values of 18.6 (HeLa), 27.7 (A549), 32.9 (MCF-7), 37.5 (Vero) μg/mL	[64]
Brazil	Leaves	26	98.6	Safrole (85.0%), terpinolene (5.4%)	**Amoebicidal:** At conc. of 0.5 mg/mL, the oil was lethal to 100% of the *Acanthamoeba polyphaga* trophozoites	[65]
Brazil	Leaves/ twigs	24	98.0	Safrole (77.9%), terpinolene (8.8%), bicyclogermacrene (3.7%)	**Antifeedant:** EC_{50} values of 0.4 and 17.7 μg/cm^2 against *L. decemlineata* and *S. littoralis*, respectively	[66]
Brazil	Leaves	7	96.1	Safrole (89.9%), terpinolene (3.10%), β-bisabolene (1.70%)		[67]
Brazil	Leaves/ twigs	22	99.4	Safrole (64.3%), terpinolene (10.2%), (*E*)-β-ocimene (5.6%),		[68]

5. Biological activities

5.1. Antioxidant activity.

Research by Caceres *et al.* [69] reported the antioxidant activity by total phenolics, DPPH, and ABTS assays. In DPPH, the methanol extract of *P. hispidum* showed IC_{50} values of 0.404 mg/mL (leaves) and 0.317 mg/mL (roots), whereas the dichloromethane extract gave IC_{50} values of 0.391 mg/mL (leaves) and 0.263 mg/mL (roots), respectively. As for ABTS, the methanol extract demonstrated IC_{50} values of 0.498 mg/mL (leaves) and 0.131 mg/mL (roots), whereas the dichloromethane extract gave IC_{50} values of 0.158 mg/mL (leaves) and 0.164 mg/mL (roots). It is also reported that dichloromethane leaves extract revealed the highest phenolic content with 14.28 µg of gallic acid/mg extract.

5.2. Antibacterial activity.

P. hispidum has several medicinal properties and harbors a diversity of endophytes. Previously, four endophytic fungi from *P. hispidum* were used for obtaining crude ethyl acetate extracts that were tested against *Enterococcus hirae*, *Escherichia coli*, *Micrococcus luteus*, *Salmonella typhi*, and *Staphylococcus aureus*, using the cup plate technique. All bacteria were inhibited by the four extracts tested, except for *Enterococcus hirae* that was inhibited by only two extracts. The extract produced by *L. theobromae* was statistically the most effective against all bacteria except for *S. typhi*, being the extract of the Diaporthales endophyte more effective against it [70].

5.3. α-Amylase activity.

Orlandelli *et al.* [71] had evaluated the suitability of four agro-industrial wastes (corncob, pineapple peel, sugarcane bagasse, and wheat bran) as low-cost substrates for the α-amylase production by nine *P. hispidum* endophytes belonging to the genera *Bipolaris*, *Colletotrichum*, *Diaporthe*, *Phoma*, *Phyllosticta*, *Marasmius*, *Phlebia*, and *Schizophyllum* by using the starch-iodine method. Their study revealed that starchy substrates were less efficient than cellulose-rich substrates. Meanwhile, remarkable results were obtained for *Bipolaris* sp. JF767001 (4.14 U/mL) cultivated with pineapple peel, and for *Phlebia* sp. JF766997 (4.09 U/mL) and *S. commune* JF766994 (4.07 U/mL) with sugarcane bagasse.

5.4. Insecticidal activity.

Dos Santos *et al.* [72] evaluated the insecticidal and repellent potential of the acetonic leaf extract of *P. hispidum* on *Hypothenemus hampei* insects by topical application, contaminated surface, and repellent effect. They found that in the exposition in the contaminated surface, 100% of mortality was observed in the dilution of 25.0 mg/mL and 50 to 80% in dilutions of 5.0 to 0.004 mg/mL, while 0.0008 mg/mL and the control resulted in only 5% of mortality. Besides, in the topic application, 60 to 65% of mortality was observed with dilutions of 25.0 to 0.1 mg/mL. However, the repellence index was lower than the minimum value praised in the literature to consider a substance as a repellent.

5.5. Schistosomicidal effects.

The dichloromethane fraction of *P. hispidum* leaves (at 100 mg/mL) extract was found inactive in terms of mortality, number of separated worms, and number of worms with reduced motor activity [73].

5.6. Leishmanicidal activity.

The ethanolic extracts of *P. hispidum* showed leishmanicidal activity against promastigotes and axenic amastigotes of *Leishmania amazonensis* with IC_{50} values of 5.0 μg/mL and 69.0 μg/mL, respectively [19].

5.7. Larvicidal activity.

Recently, Falkowski *et al.* [74] reported the leaves extract's larvicidal activity against *Aedes aegypti* laboratory strain susceptible to all insecticides. The extract exhibiting more than 50% larval mortality after 48 h of exposition at 100 μg/mL against the natural population were considered active. The leaves ethyl acetate extract of *P. hispidum* was found active with LC_{50} values of 70.5 (95% CI 60.4–81.6) and 54.7 (95% CI 45.9–64.0) μg/mL at 24 and 48 h against the laboratory strain Paea. In another study, the ethanol leaves extract of *P. hispidum* showed larvicidal potential against *A. aegypti* larvae with an LC_{50} value of 0.169 mg/mL [75].

5.8. Antiplasmodial activity.

The lipophilic extracts of *P. hispidum* proved to be active against both a chloroquine-sensitive and a resistant strain of *Plasmodium falciparum* with IC_{50} values of 7.6 and 13.0 μg/mL, respectively [34].

5.9. Cytotoxicity activity.

The lipophilic extracts of *P. hispidum* reported moderately active against human tumor cell lines SK-MEL30 (melanoma) and MCF-7 (mamma cell carcinoma) with IC_{50} values of 24.1 and 25.1 μg/mL, respectively. Meanwhile, the extract was found inactive against KB (squamous carcinoma) and A549 (lung carcinoma), which gave IC_{50} value >30 μg/mL [34].

5.10. Estrogenic and serotonergic activities.

Michel *et al.* [36] reported the *P. hispidum* leaf extract enhanced the expression of the estrogen-responsive reporter and endogenous genes in MCF-7 cells, demonstrating estrogen agonist effects.

6. Conclusions

In conclusion, the knowledge of traditional usages, origin, phytochemicals, and biological activities on *P. hispidum* has been comprehensively studied and have been well supported and clarified by modern pharmacological studies. Thus, it is suggested the potential application of *P. hispidum* on health and pharmaceutical industry. However, the present findings are still insufficient as the study of action mechanisms is still not clearly identified. Therefore, further efforts are needed, and more well-designed studies both in vitro and in vivo are required to establish the possibilities of *P. hispidum* to be used as a food supplement or for pharmaceutical purposes.

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Conflicts of Interest

The authors declare no conflict of interest.

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