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A Phytochemical and Ethnopharmacological Review of the Genus Piper: as a Potent Bio-Insecticide

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Review

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ABSTRACT

The genus Piper is of great significance to a commercial and economic level into the flavoring, pharmaceutical and insecticide industry, and great traditional use. Some species of this genus have been well explored. The aim of this review is to provide comprehensive information in the fields of Botany, traditional uses, phytochemistry and pharmacology of the genus Piper in order to explore its therapeutic potential and future research opportunities as a possible bio-insecticide in Mexico. All the available information material about the genus Piper was collected via electronic research: Pubmed, SciFinder, Scirus and Google Scholar; also a library research for articles published in peer-reviewed journals, thesis and books.

Several species of the genus Piper were found in Mexico and they are used ethnomedically, such as *Piper auritum*, *Piper aduncum* L. H.B. & K.; *Piper nudum* C. DC., *Piper hispidum* Swartz, *Piper sanctum* Schiltdl. ex Miq., *Piper umbellatum* L., *Piper psilorhachis* C. DC., *Piper diandrum* C. DC., and *Piper amalago* L. Phytochemical research on Piper genus has found alkaloids, pterocarpans, sterols, flavonoids, triterpenoid, saponines, phenylethylamines and amines. The genus Piper have showed a wide spectrum of pharmacological activities *in vitro* and *in vivo*, and insecticide activities. However, there is a need to research for individual secondary metabolites responsible of these actions, and to study the way they act, as well as physiological pathways in detail. Piper has emerged as a good source of traditional medicine and it exhibits a wide spectrum of pharmacological activities and among other biological properties, who could be a possible bio-insecticide in Mexico.

INTRODUCTION

Piperaceae family contains a wide variety of species; they group together into fourteen genuses and between 1950 and 2000 species approximately [1,2]. The genus Piper includes a numberless of bushes, herbals and ivies that can be found in hushed and humid places all around the globe; for instance, jungles and rain forests [3] of tropical regions of both hemispheres [4], the most known the genus *Piper*aceae family species that distribute in tropical and subtropical regions of the world are Piper *and Peperomia*, which include 600 and 700 species approximately. Although the largest number of Piper species are found in America (around 700 species) and Southern Asia (about 300 species), a smaller number of species are found in the South Pacific (about

140 species) and Africa (around 15 species) [5-8] . Among them, many species of the genus Piper are considered economical and ecologically important.

For example, the specie *Piper auritum* has been used for different gastronomy and medicinal purposes. Medicinal applications embrace; in case of fever; as a perspiratoy, diuretic and stimulant; erysipelas, gout, sore throat, and local anesthetic. It is also used as treatment for gonorrhea, bellyaches, headaches, wound poultice and repulsive and digestion stimulant as well [9]. Anti-inflammatory, anti-bacterial and anti-fungal activities have also been reported [10-12]. This species is easily recognized by its large (20-50 cm) leaves, which are unequally lobed at the base and the very characteristic sarsaparilla or anise-like odor of its crushed leaves. Other studies in the literature have reported that Piper species have anti-leishmanial activity [13] and their essential oils have become an important aim in the search of new anti-parasite treatments.

The confirmed biological activity of some the genus Piper species is due to a wide variety of alkaloids, amides, propenyl phenols, lignanes, terpenes, flavonoids [14,15], among other compounds, which are biologically active against pathogen agents that affect human wellbeing **(Tables 1 and 2).** Nevertheless, it is still missing to carry out some investigations about diversity of this genus present in Mexico, taking into account the large number and the global size of these species in the world. The aim of this review is to provide comprehensive information on Botany, traditional uses, phytochemistry and pharmacology research of the genus Piper to explore its potential benefits and future research opportunities as a possible bio-insecticide in Mexico.

Table 1. Some secundary metabolites and biological activities of the genus Piper species.

Species	Secondary Metabolites	Biological activity
Piper hispidum	Amides	Anti-fungicide against Cladosporium sphaerospernum [22]
Piper tuberculatum	Amides	Anti-fungicide against Cladosporium sphaerospernum [22]
	Isobutìllical amides and Piperidìnical	Biocide action against Cladosporium sphaerospermun and Cladosporium cladosporioides [27]
Piper sarmentosum	Alkaloids	Anaelgesic, anti-inflamatory, anti-cancerous [3,32]
Piper capense	Alkaloidal amides	Anti-parasite [39]
Piper dilatatum	Chalcons and derivates from benzoic acid	Anti-fungicide against Cladosporium sphaerospernum [51]
Piper chaba	Amides and alkaloids	Hepato protective [17,41]
Piper kadsura	Neolignanes	Anti-neuroinflammatory [39]
Piper longum	Amides	Insecticide – acaricide [26]
Piper tricuspe, Piper gorgonillense and Piper hispidum	β-cariophyllene, α-Selinene,	Bacillus subtilis, Staphylococcus aureus [22]

Table 2. Biology activities of the genus Piper by organism groups.

Piper	Organisms group	Specie	Biology activities
P. nigrum	Mammals	Mus musculus	Antifertily [30]
P. eriopodon, P. bredemeyeri, P. brachypodom, P. auritum, P. var brachypodom, P. septuplinervium, P. lanceifolium, P. cf. brachypodom, P. bogotense, P. cf. Divaricatum, P. var brachipodom, P. marginatum, P. diandrum, P. peltatum, P. dondell smithll, P. umbellatum y P. jacquemontianum	Arthropod	*Artemia franciscana*	Citotoxity [27,28]
P.r aduncum, P. auritum, P. longum, P. ribesoides, P. sarmentosum	Arthropod	*Aedes egypti*	Insecticida [44]
P. nigrum, P. tuberculatum, P. guineense	Arthropod	*Malacosoma americanum*	Insecticidal [15]
P. nigrum, P. guineense, P. tuberculatum	Arthropod	*Neodiprion sertifer*	Insecticidal [15,20]
P. aduncum, P. nigrum	Arthropod	*Musca domestica*	Insecticidal and Repellent [2]
P. nigrum, P. grande	Arthropod	*Drosophila melanogaster*	Insecticidal [2,26]
P. crassinervium, P. aequale	Arthropod	*Rhipicephalus (Boophilus) microplus*	Insecticidal [12]
P. nigrum, P. tuberculatum, P. aduncum	Arthropod	*Diatrea saccharalis*	Insecticidal [17]
P. eriopodon, P. umbellatum, P. pesaresanum	Arthropod	*Hyphothenemus hampei*	Insecticidal [14]
Piper tuberculatum	Arthropod	*Aedes aegypti L.* and *Anopheles pseudopunctipennis Tehobal*	Insecticidal [12]
P. nigrum	Arthropod	*Spodoptera frugiperda*	Insecticidal [17]
P. betel, P.sanctifelis, P. auritum, P. aduncum	Fungi	*Apergilus flavus*	Fungicide [52]
P. betel, P. ovatum, P. tuberculatum.P. arboreum	Fungi	*Candida albicans*	Fungicide [32]
P. betel	Fungi	*Fusarium oxysporum*	Fungicide [21]
P. betel, Piper ovatum	Bacterial	*Staphylococcus aureus*	Bactericide [41]
P. lanceifolium	Bacterial	*Salmonella tiphy Klebsiella pneumoniae Pseudomona aeruginosa, Escherichia coli*	Bactericide [32]

Botanical description of the genus Piper

The genus Piper includes: 1000 species making it one of the largest genera of basal angiosperms [16,17]. They are characterized by their alternate leaves, opposed inflorescences, rarely axillary, single or compounds, floral bract deltoid, triangular, occasionally smooth, glossy, densely clustered flowers on the vertical axis, anthers opening in a vertical, horizontal, or oblique plane; pistil 3-5 carpels, smooth fruit, stylish, depressed or truncated [18]. Distribution patterns of the genus Piper species vary from being locally endemics until to spread out. There are several species restricted to a specific center of diversity (e.g. Andes, Central America) and others occur throughout neotropics or paleotropics [8,19] in neotropics can be found around 800 species, mainly in the Pacific Coast of Colombia and Ecuador, the Peru's Amazonian West and North. The Brazil's Atlantic Coast, the Venezuela's Andes, the South of Mexico, such as Veracruz and the Yucatan peninsula [20].

In the region of Tuxtla, Veracruz, Mexico; Species of the genus *Piper* were found and identified including: *Piper aduncum* L., *Piper aequale Vahl*, *Piper aereum Trel*., *Piper amalago* L., *Piper auritum Kunth*, *Piper berlandieri* C. DC., *Piper diandrum* C. DC., *Piper dilatatum Rich*, *Piper hispidum* Sw., *Piper lapathifolium* C. DC., *Piper obliquum* Ruiz & Pavon. (Synonyms for the *Piper peltatum* and *Piper umbellatum* L.) [8], *Piper Peracuminatum* C. DC., *Piper pegamentifolium* Trel. & Standl., *Piper sanctum* (Miq.) Schltdl. ex C. DC., *Piper scabrum* Lam., *Piper Schiedeanum* Steud., *Piper yzabalanum* C. DC.; and *Piper berlandieri* C. CD. (Natural Reserve's Biology Station Los Tuxtlas, San Andres Tuxtla, Catemaco, Sierra de Santa Marta; Schouppe) [21]. Other species is *Piper hispidium* Swingle, it is a native shrub of Mexico's lowlands, a species of pan-tropical distribution, commonly found throughout forest sites. It is also commonly known as "cordoncillo" Around Xalapa city, Veracruz, Mexico and Colombia [22]. Others nine species of the genus Piper were reported in Xalapa city, Veracruz, Mex., such as: *Piper umbellatum*, *Piper hispidum*, *Piper sanctum*, *Piper aduncum*, *Piper auritum*, *Piper amalago*, *Piper psilorhachis*, *Piper diandrum* and *Piper nudum* [23].

Traditional uses of the genus Piper

Ethnopharmacology and phytochemical constituents

Chemical investigations have revealed the presence of isoflavones, isoflavanones, C-glucosyl, flavonoids, and pterocarpanes, as well as alkaloids, amides, propenyl phenols, lignanes, neolignanes, terpenes, steroids, piperloids, chalcones, dihydrochalcones, flavones and flavanones in the genus Piper [3,34]. Secondary metabolites have been found in all parts of the plant, including leaves, stems, roots, and inflorescences [25]. Although all species investigated produce mixtures of secondary metabolites and some particular species contain very diverse suites of secondary metabolites (e.g., *P. nigrum*, *P. betle*, *P. auritum*), only a few studies have tested for the additive or synergistic interactions that may exist between these compounds [35-37] **(Figure 1).**

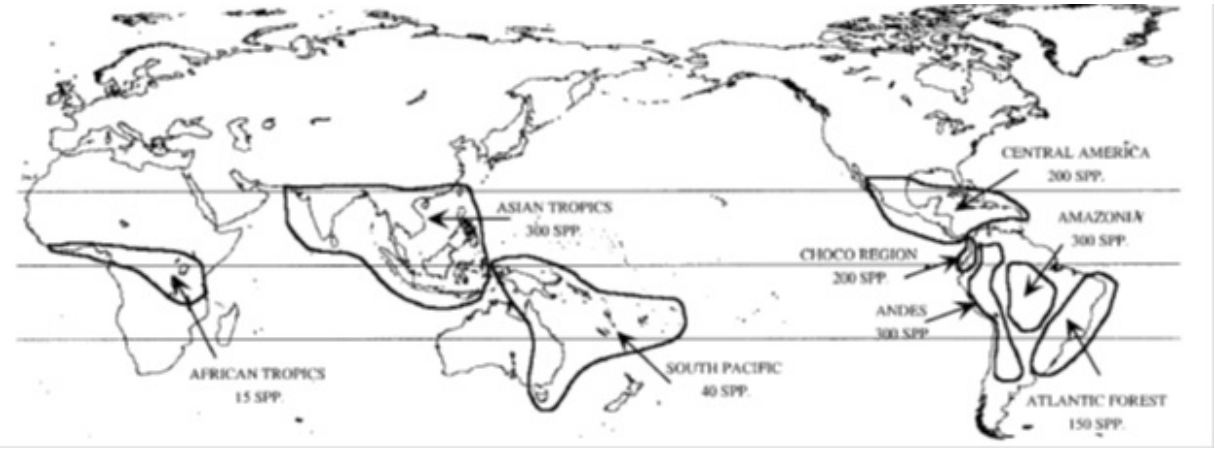

Figure 1. Geographic distribution of the genus *Piper* species. Numbers are estimations for each one of the diversity centers, thus, locally taxa may be represented more than once (Taken from Jaramillo and Manos, 2001).

Also, in some others species of the genus Piper various compounds have been purified and isolated by chromatographic techniques [9,15], which have characterized some of them using different spectroscopic methods, such as: infrared spectrum (IS) mass spectrometry (MS) and the distinct nuclear magnetic resonance (NMR) techniques. Piperine **(Figure 2)** was the first amide to be isolated from Piper species [25,34].

Among *Piperaceae* family, for instance, *Piper aduncum* is the most chemically investigated species and several bioactive alkaloids, chromenes, dihydrochalcones, flavonoids, and benzoic acid derivatives have been described. In *Piper aduncum's* essential oils L (*sinonymus: Piper cettidifolium* Trel) has been reported the presence of 5-metoxi-6-(2'-propen)-benzodioxole, dillapiole, etoxidillapol, miristicine and piperitone. Also in fruits were found 4-metoxi-3,5-bis (3'-methyl-but-2'-en-1'1)-benzoic acid, chalcons, pseudo dillapiol and pinostrobin. Alternatively, in leaves were found dillapiol and camphor [30]. *Piper aduncum* EtOH extract from leaves has given three prenylated methyl benzoates including the new methyl 4-hydroxy-3-(20-hydroperoxy-30-methyl-30-butenyl) - benzoate, one flavanone, and two chromenes [38].

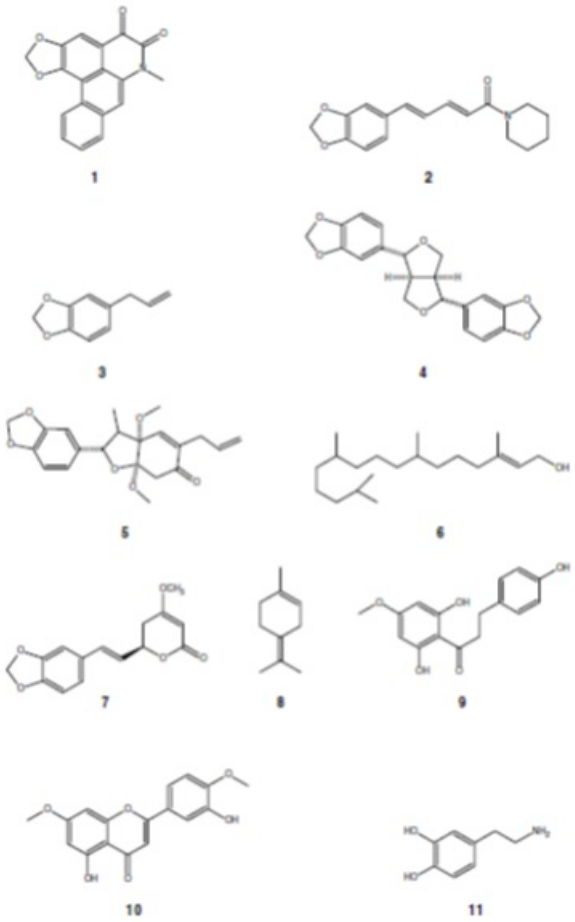

Figure 2. Examples of major classes of compounds found in Piper spp. Stereochemistry is depicted in all cases for which it is known. Amides: cepharadione A (1) and piperine (2, first amide isolated); Propenylphenol: safrole (3); Lignan: sesamin (4); Neolignan: kadsurin A (5); Terpenes: transphytol (6), terpinolene (8); Kawapyrone: methysticin (7); Dihydrochalcone: asebogenin (9); Flavone: 7,4′-dimethoxy-5,3′-dihydroxyflavone (10); Other: dopamine (11), (Taken from Dyer et al., 2004).

In terms of chemical constituents, the *Piper hispidumis* plant reported to contain amides, benzenes, benzoic acids, flavonoids, and volatile oils, which have shown significant anti-fungal, anti-microbial, anti-plasmodial, leishmanicidal and insecticidal activities. Three butenolides including a new compound like 9, 10-methylenedioxy-5, 6-Z-fadyenolide have been isolated from *Piper hispidum* leaves and its structures have been determined. Also, it has been found that *Piper hispidum* leaf extracts have enhanced the estrogen expression reporter responsive and endogenous genes in MCF-7 cells, demonstrating estrogen agonist effects. *Piper hispidum* extracts have also acted as agonists of the ER and 5-HT7 receptors [39].

Piplartine (5,6-dihydro-1-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-2(1H) pyridinone) is an amide alkaloid compound of Piper species. This secondary metabolite has significant cytotoxic activity against tumor cell lines, especially human leukemia cell lines, such as HL-60, K562, Jurkat, and Molt-4, as well as anti-fungal, anti-platelet aggregation, anxiolytic and anti-depressant properties. This is an isolated molecule from *Piper tuberculatum* [40,41].

Also, these amides have generated interest as a result of their potent insecticidal and antifungal properties. Structures of several anti-fungal amides are: N-[7-(30, 40-methylenedioxyphenyl)-2(Z), 4(Z) heptadienoyl] pyrrolidine, (3Z, 5Z)-N-isobutyl-8-(30, 40-methylenedioxyphenyl)- heptadienamide they have been isolated from *Piper hispidum* leaves and 8(Z)-N-(12, 13, 14-trimethoxycinnamoyl)-3-pyridin-2-one, from *Piper tuberculatum* besides eight known anti-fungal amides have already been reported. Two new amides which are N-[10-(13, 14-methylenedioxyphenyl)-7(E), 9(Z)- pentadienoyl]-pyrrolidine, arboreumine and nine known anti-fungal amides N-[10- (13, 14-methylenedioxyphenyl)-7(E)-pentaenoyl]-pyrrolidine, its derivative N-[10-(13,14 methylenedioxyphenyl)-pentanoyl]-pyrrolidine and N-[10-(13, 14 methylenedioxyphenyl)-7(E),9(E)-pentadienoyl]-pyrrolidine; besides pellitorine, abdihydropiperine, piplartine, dihydropiplartine, cis-piplartine (or 8(Z)-N-(12,13,14-trimethoxycinnamoyl)-3-pyridin-2-one) and fagaramide have also been reported recently [42-47].

Recently, in Veracruz, Mexico was reported a study about the preliminary phytochemical characterization in nine species of the genus Piper which were identified (Mayer, Grangendorff and Wagner's tests) alkaloids in nine species, highly present in *Piper umbellatum* and *Piper hispidum*, FeCl2 and Shinoda tests were used and in six species flavonoids were identified. *Piper sanctum*, *Piper hispidum* and *Piper aduncum* showed a lower intensity to the flavonoids presence and *Piper unbellatum* the one which presented a higher intensity to the flavonoids presence. However, it was detected triterpenes and/or sterols in the nine species as well (Lieberman-Bouchard's test) observing rings of bigger intensity in *Piper auritum*, *Piper aduncum*, *Piper umbellatum*, and

Piper amalago followed by *Piper psilorhachis* and *Piper hispidum* and in lower intensity, *Piper sanctum*, *Piper diandrum*, and *Piper nudum*. Saponines tests (foam and Lieberman) resulted negative to the nine species. Finally, cumarines presence (fluorescence test) was found in *Piper psilorhachis*, *Piper umbellatum*, *Piper hispidum* and *Piper nudum* [23].

There are reports about various Piper species where it has been observed compounds structurally alike to the prenylated benzoic acid, in the case of *Piper aduncum* [38] it was found an anti-microbial and molluscicidal activity [48,49]. In *Piper arieianum*, *Piper tabogatum* and *Piper dilatatum* which they also contain prenylated benzoic acids showed fungicidal activity [50-52], found a moderate activity anti-plasmodial and had a low cytotoxic activity, for extracts of species, such as: *Piper aduncum* L, *Piper auritum Kunth*, *Piper jericoense* Trel. and Yunck, *Piper obrutum* Trel. and Yunck, *Piper marginatum* Jacq **(Tables 1 and 2).**

All this information, confirms that the genus Piper contains potentially active compounds that could be investigated in several biological methods to prove their curative effectiveness and efficacy against pathogen agents. Other derivative metabolites that were isolated in a variety of the genus Piper species were reported years ago, where 600 chemical compounds coming from different types of bioactive compounds were descripted approximately (See paper: phytochemistry of the genus Piper by Parmar [34].

CONCLUSION

The Piper species chemistry has been widely investigated and the phytochemical investigations from the entire world have led to the isolation of a number of compounds physiologically active like: alkaloids, amides, propenyl phenols, lignanes, neolignanes, terpenes, steroids, kawapyrones, piperloids, chalcons, dihydrochalcones and flavones. Biological activities of different species have had special emphasis, while it exhibits a wide spectrum of pharmacological activities. Also Piper has emerged as a good source of traditional medicine and promising results should be further substantiated by clinical treatments and future research opportunities as a possible bio-insecticide in Mexico. However, there is a need to research for individual secondary metabolites responsible of these actions, and to study the way they act, as well as bioavailability, pharmacokinetics and physiological pathways in detail for Mexico.

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