International Journal of Phytocosmetics and Natural Ingredients 2014;1:4

doi 10.15171/ijpni.2014.04

Review Article

Importance of a multidisciplinary evaluation of Piper genus for development of new natural products in Latin America

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Received 13 Mar. 2014
Accepted 23 June 2014
ePublished 17 Sept. 2014

Abstract

Piper species are basal angiosperms used by men as condiment and medicine since ancient times, and can be easily found in tropical and subtropical forest of America. This mini review article deals with the potential of this genus as a source of new natural and bioactive compounds. The large chemical diversity in *Piper* species encompasses the volatile components with frequent occurrence of phenylpropanoids besides terpenes, but also some specific classes of compounds such as amides, piperolides, kavalactones, chromenes and benzoic acid derivatives. Additional classes include lignans, neolignans and also flavonoids. *Piper nigrum* is the most known species because of its use as spices and also as medicinally all over the world for many centuries. Since several studies have been conducted on wild species of this genus in Latin America, this review summarize the bioactivity observed for 36 species, including biocidal (antibacterial, antifungal, antiprotozoal, antiviral, larvicidal, acaricidal and cytotoxic), antioxidant, cyclooxygenase inhibitors, anti-inflammatory, anti-ulcerogenic, anti-myotoxic, anxiolytic, estrogenic and serotonergic activities. Considering the task to examine over 1000 species of *Piper*, a multidisciplinary and international network is proposed to study topics covering the ethnobotany to the chemistry and bioactivity with the hope to contribute to the discovery of new natural products from biodiversity.

Keywords: Basal angiosperms, Biodiversity, Bioactivity, Bioprospecting, Secondary compounds

Introduction

Piper species have been utilized by men as condiment and medicine since ancient times. This is one of the most important genera of spicy plants from tropical forests of the Americas.[1] Until 1980 all the information on this genus resulted from studies made on Indian species, but since then the large proportion of the information has been generated from Latin American species. Such studies have pointed out to an enormous diversity of chemical compounds associated to various biological activities for these species. One major motivation for these studies is the high density of *Piper* species in both understory and secondary vegetation. Besides, the interaction with disperser animals such as bats or with caterpillars and beetles has indicated *Piper* as an important model species to investigate tropical ecology.[2]

A survey of the native *Piper* species to Central and South America with potential application due to its bioactivity and chemical composition showed that at least 38 species yielded interesting results and should be further investigated. The great potential associated to the large number of research groups working on this subject encouraged us to propose the creation of an international network devoted to a multidisciplinary assessment of this genus, with the aim of integrating efforts among researchers in order to discover new natural products with potential use.

The genus *Piper*

The genus *Piper* has more than 1000 species which is an impressive diversification among basal Angiosperms. The species included in this genus are rather uniform morphologically, with simple, alternate leaves and joined stems with enlarged nodes; many produce pearl bodies on the leaves or stems, but the most distinctive morphological feature is the production of inflorescences, which contain dozens (*P. garagaranum*) to thousands (*P. auritum*) of tiny seeds packed into upright or pendant spikes.[3] Although very few have important global economic value, many of them are important for its wide utilization by native populations as medicine and culinary purposes.

The main representative is *P. nigrum*, black-pepper or "king of spices", has about 51 cultivars reported from the tropical and subtropical regions of India, as well as *P. betle* and *P. longum,* which are one of the most consumed condiment due to its pungent properties, but it is also used as medicine, preservative, and biocontrolling agent. Preparations from black-pepper or its main active amide, piperine, can stimulate the digestive enzymes improving digestion in general and preventing some diseases of

Please cite this paper as: Cáceres A, Kato MJ. Importance of a multidisciplinary evaluation of *Piper* genus for development of new natural products in Latin America. International Journal of Phytocosmetics and Natural Ingredients 2014;1:4. doi: 10.15171/ijpni.2014.04

this organ, but it also has displayed anti-inflammatory, thermogenic, growth stimulatory, anti-thyroid and chemopreventive activities.[4] The economic value of black-pepper is estimated in several millions of dollars in the international market.[5]

Besides the morphological uniformity, the genus is well known for its chemical pharmacological diversity. The biogeography of the genus indicates a great diversity in the American continent, where three biogeographic provinces: Central America, Mexico and Colombian northwest, the Amazon basin and the Atlantic forest of Brazil were described.[6]

Finally, the study of diversification of basal Angiosperms is of great importance to understand part of the process involved in biological diversification. The variety of ecological interactions includes predation of leaves by caterpillars and beetles or seed dispersal by bats. The variety interactions may be one of the driving force for its high and complex botanical, chemical and biological diversity of *Piper* species.

Chemistry and pharmacology of *Piper* species from Latin American

Chemical analysis of volatile constituents have indicated the occurrence of monoterpenes and sesquiterpenes but also some phenylpropanoids such as safrol, dillapiole, myristicin and elemicin with interesting biological properties.[7-11] The essential oil varies from species to species and several studies addressed to evaluate their properties or composition were described.[12-15] The phytochemical analysis of extracts demonstrated the presence of a large variety and specific classes of compounds, such as amides, chromenes, piperolides, kavalactones and derivatives.[16-20] Besides, the frequent occurrence of lignans, neolignans, steroids, chalcones, flavones and flavanones has also been described.[22-25]

Until 1980 most of the information on *Piper* genus came from the Asian continent, particularly from India, showing diverse chemistry, and besides its culinary and aromatic characteristics, several pharmacologic activities has been demonstrated,[4] particularly antioxidant[26,27] and cyclooxygenase inhibitors.[28,29] But in the last decade's most of the information has resulted from studies made in Latin America. The antioxidant activity has been particularly investigated. For instance, the activity of hydroquinones from *P. crassinervium*[30], as well as extracts, essential oils or fractions from *P. auritum*[31], *P. aduncum*[32], *P. peltatum*[33], *P. sanctifelisis*[20], *P. subpedale*[34], *P. imperiate*[35] and *P. jacquemontianum*[36] have indicated the potential of *Piper* species.

Another field where research is ample in Latin America is the biocidal activity. Activity against several bacteria has been demonstrated in leaves and roots of *P. regnelli*[37,38], and leaves of *P. marginatum*[39], *P. tricuspe* and *P. gorgonillense*[40], as well as activity against *Helicobacter pylori* by *P. multiplinervium*[41] and *P. carpunya*[42], and against *Mycobacterium tuberculosis* by *P. imperiale*.[35]

Activity against human and plant fungal pathogens have been demonstrated in several species such as *P. hispidum*[43], *P. auritum*[44], *P. malacophyllum*[45], *P. regnellii*[46], *P. aduncum*[47], *P. mollicomum*[13], *P. hispidinervum*[48], and *P. gaudichaudianum*.[49]

The activities against various protozoa of public health importance to the tropics, like *Leishmania, Plasmodium* and *Trypanosoma* have also been studied. The most active compounds isolated from *Piper* species are the prenylated benzoic acid derivatives, found in *P. heterophyllum* and *P. aduncum,* which demonstrated activity to several protozoa (IC_{50} 6.5 µg/ml).[50] Additional *Piper* species with activity against protozoa include *P. regnellii*,[51] *P. arboreum, P. tuberculatum*[52,53], *P. cumanense, P. holtonii*[54], *P. auritum*[55], *P. hispidum*[56], *P. friedrichsthalii*[57], *P. aduncum, P. jericoense*[58], *P. jacquemontianum, P. variabile*[15] and *P. malacophyllum*[59]. Antiviral activity has also been described for *P. regnelli*.[60]

Other biocidal effect include the activity of essential oils or extracts from different species, such as the insecticidal activity of *P. aduncum* and *P. hispidinervum* on *Tenebrio molitor*[61] and *Spodoptera frugiperda*[62], of *P. hispidum* on *Hypothenemus hampei*[63], and of *P. aduncum* on *Musca domestica*[64]; the larvicidal and oviposition deterrent of *Aedes aegypti* by *P. krukoffii* and *P. marginatum*[14], and the acaricidal activity of *P. amalago, P. mikanianum* and *P. xylosteoides* on *Rhipicephalus microplus*[65] and of *P. aduncum* on *Varroa destructor*.[66]

Important biocide activity has also been assessed for the cytotoxic activity, which was demonstrated against *Artemia salina* or different cancer cell lines by *P. artanthe*[67], *P. imperiale*[35], *P. variabile*, *P. jacquemontianum* (CI_{50} <10 µg/mL)[15] and *P. auritum*[58], as well as the *in vitro* and *in vivo* activity of extracts, fractions and eupomatenoid-5 of *P. regnellii*.[68]

Other interesting activities demonstrated by *Piper* species from tropical America include the anti-ulcerogenic activity of flavonoids from *P. ossanum*[69]; myotoxic phospholipase inhibitory activity on *Bothrops* venom by 4-nerolidilcatechol isolated from *P. umbellatum* and *P. peltatum*[70]; the anti-secretory and anti-inflammatory activity of fractions isolated from *P. carpunya*[42]; the anti-nociceptive and anti-inflammatory activity of the essential oil of *P. ovatum*[71] and *P. aleyreanum*[72]; the anxiolytic and anti-depressant activity of piplartine isolated from *P. tuberculatum*[73] and other amides from *P. amalago* and *P. mikanianum*[74]; the estrogenic and serotonergic activity of butenolides isolated from *P. hispidum*[75]; the anti-inflammatory activity of dillapiole isolated from *P. aduncum*[76], and other activities that propose an enormous potential of this genus in the search for new treatments for human, animal and plant diseases (Table 1).

Proposal of an international network

The RIBIOFAR network from CYTED, evidenced that several activities for the assessment of medicinal

Table 1. Bioactivity and chemical composition of selected Latin American Piper species

Species	Bioactivity	Chemical composition	References
P. aduncum	AC, AF, AO, AP, IN	Dillapiole, EO, FL, PPC, pinocembrin	Fazolin et al.[61]; Navickiene et al[47]; Leyva et al.[64]; Ramos et al.[32]; Flores et al.[50]; Parise-Filho et al.[76]; Pino et al.[66]; Mesa et al.[58]
P. aleyreanum	AI	EO	Lima et al.[72]
P. amalago	AC, AD	Amides, EO, FL	Ferraz et al.[65]; Lopes et al.[74]
P. arboreum	AP	Amides	Regasini et al.[52]
P. arthante	CT	EO	Avella and Rios Motta[67]
P. auritum	AO,AF,AP,CT	EO, fractions	Hernández Diaz et al.[44]; García Rios et al.[31]; Monzote et al.[55]; Mesa et al.[58]
P. caldense	AF	PHBA	Freitas et al.[80]
P. carpunya	AB, AI, AM	Fractions	Quílez et al.[42]
P. claussenianum	AP	EO (nerolidol)	Marques et al.[81]
P. crassinervium	AO	Hydroquinones	Yamaguchi et al.[30]
P. cumanense	AP	Fractions	Sánchez-Suárez et al.[54]
P. elongatum	AP	EtOH	Flores et al.[79]
P. friedrichsthalii	AP	EtOH	Chinchilla-Carmona et al.[57]
P. gaudichaudianum	AF	EO	Morandim-Gianneti et al.[49]
P. gorgonillense	AB	EtOH	Pino Benitez[3]
P. heterophyllum	AP	PHBA	Flores et al.[50]
P. hispidinervum	AF, IN	EO EtOH extract	Fazolin et al.[61]; Zacaroni et al.[48]
P. hispidum	AP, IN, estrogenic	EtOH, amides, butenolides	Alécio et al.[43], Michel et al.[75]; Santos et al.[63]; Ruiz et al.[56]
P. holtonii	AP	EtOH,fractions	Sánchez-Suárez et al.[54]
P. imperiale	AB, AO, CT	PHC	Diaz et al.[35]
P. jacquemontianum	AO, AP, CT	EO, EtOH extract	Cáceres et al.[36]; Cruz et al.[77]
P. jericoense	AP	EtOH	Mesa et al.[58]
P. malacophyllum	AF, AP	EtOH, piperolides	Lago et al.[45]; de Oliveira et al.[59]
P. marginatum	AB IN	EO, EtOH, FL	Duarte et al.[39]; Autran et al.[14]
P. mikanianum	AC, AD	Amides, EO, FL	Ferraz et al.[64]; Lopes et al.[73]
P. mollicomum	AF	Chromenes	Lago et al.[16]
P. multiplinervium	AB	PHBA	Rüegg et al.[41]
P, ossanum	Anti-ulcerogenic	EtOH,FL	Apecechea-Coffigny et al.[69]
P. ovatum	AI	Fractions, amides	Rodrigues Silva et al.[71]
P. peltatum	AM, AO	4-nerolidylcatechol	Nuñez et al.[70]; Puertas-Mejía et al.[33]
P. regnellii	AB, AF, AP, AV, CT	EtOH extract, fractions eupomatenoid-5	Pessini et al.[37]; Nakamura et al.[51]; Felipe et al.[38]; Longato et al.[68]; Bertol et al.[60]
P. sanctifelisis	AO	EO	Olivero-Verbal et al.[20]
P. solmsianum	AP	EO, LIG	Morandim-Gianneti et al.[49] Martins et al.[82]
P. scutifolium	AF	Amides	Marques et al.[18]
P. subpedale	AO	Organic extracts	Mesa et al.[34]
P. tricuspe	AB	EtOH	Pino Benitez[40]
P. tuberculatum	AD, AP, CT, M	Amides, piplartine	Felipe et al.[73]; Regasini et al.[52]; Rapado et al.[53]; de Moraes et al.[78]
P. umbellatum	AM	4-nerolidylcatechol	Nuñez et al.[70]
P. variabile	AP, CT	EO, EtOH	Cruz et al.[15]
P. xylosteoides	AC	EO, amides	Ferraz et al.[65]

Bioactivity: AB, Antibacterial; AC, Acaricidal; AD, Anti-depressant/anxiolytic; AF Antifungal, AI: Anti-inflammatory; AM, Anti-myotoxic; AO, Antioxidant; AP, Antiprotozoal; AV, Antiviral; CT, Cytotoxic: IN, Insecticide/larvicide; M: Molluscicide; Chemical composition: EO, Essential oil; EtOH: Ethanol extract; FL, Flavonoids; LIG, Lignans; PHBA, Prenylated hydroxybenzoic acid derivatives; PPC, Polyphenolic compounds

plants from the Latin American biodiversity were being conducted. Nevertheless, very often the multidisciplinary activities on *Piper* genus are scarce. Thus, at the final meeting (Itajai, Brazil, October 2010) it was decided that a survey on interest to organize a specific network in Latin America should be made. An invitational letter was sent to detected research groups working on various aspects of *Piper* species and during 2010-11, 26 groups from 11 countries, including 82 researchers responded to the call, and registered as members. The expertise indicated by these groups covered chemistry (16, 62%), biomedicine (5, 19%) and botanical-agronomical (5, 19%) aspects and the scientific production included more than 160 publications since 1994.

In November 2011, during the International Symposium on Medicinal and Aromatic Plants organized by ISHS in Antigua Guatemala, a first organization meeting (1OM) was held. A working plan was established to participate in international meetings to be held during 2012 in Brazil, Colombia and Ecuador to stimulate the organization of this network. It is expected that during these meetings a network could be established in order to organize a multidisciplinary international network that eventually could prepare a proposal to be applied for funding.

As a follow up of agreed activities, four leaf sheets have been sent to registered researchers, and follow up activities were conducted in the following events during 2012:

- VI Ibero-American Symposium on Medicinal Plants, organized by RIBIOFAR-UNIVALI network held in Ponta Grossa, Brazil on June 13-15, where the conference "La subred sobre el género *Piper,* Situación actual y futura" was presented and the second organization meeting (2OM) was held 2RCI.
- V International Congress on Medicinal, Aromatic and Condiment Plants organized by the National University of Colombia was held in Palmira in September, 6-8, a forum was organized with six presentations from researchers on *Piper* species and the 3OM was held with the participation of six Colombian institutions.
- XXII Symposium on Medicinal Plants of Brazil, organized by the Federal University of Rio Grande do Sul, was held in Bento Gonçalves on September, 18-21, a forum showing the present trends in the research of this species took place and the 4OM was held with the participation of eight Brazilian institutions.
- II International Symposium on Medicinal Plants and Natural Products, organized by ISHS-SHMEN took place in Quito, Ecuador on December 5, where a presentation on the importance of study of genus *Piper* in South America was held; three Ecuadorian institutions were detected to be working with this species.

Main activities of the network are: Inventory of *Piper* species from Latin America, organization of database on agronomical, phytochemical and pharmacological studies, cooperation activities among interested researchers for increasing the knowledge on these species, and facilitate development of new products for national or international markets. In conclusion, an Ibero-American Network for the multidisciplinary evaluation of *Piper* genus is proposed in order to help in the integral development of new products from the rich regional biodiversity.

Conclusions

Piper is a diverse and highly interesting genus from a multidisciplinary point of view, being studied by several groups of academic researchers in Latin America. The organization of a network is proposed for the integrated study of this genus, aiming the developing of new products from the biodiversity rich countries.

Acknowledgements

To Consejo Nacional de Ciencia y Tecnología (CONCYT), projects FODECYT 17-2009 and 27-2011, and FACYT 37-2011; RIBIOFAR Network (RT 0284) from CYTED; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); and, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for financial support.

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