International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

International Journal of Pharmacology 11 (6): 523-531, 2015
ISSN 1811-7775

MINI REVIEW ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.523.531

Heteropterys Genus: A Review of its Phytochemistry and Pharmacology

[1]Maira Huerta-Reyes, [2]Rosa María Fonseca Juárez and [3]Arturo Aguilar-Rojas
[1]Unit of Medical Research in Pharmacology, Specialities Hospital, XXI Century National Medical Center, Mexican Social Security Institute, Av. Cuauhtemoc No. 330, Col. Doctores, Del. Cuauhtémoc, CP 06720, Mexico DF, Mexico
[2]Laboratory of Vascular Plants, Faculty of Sciences, National Autonomous University of Mexico, Del. Coyoacán 04510, Mexico City, Mexico
[3]Unit of Medical Research in Reproductive Medicine, UMAE Obstetrics and Gynecology No. 4 Dr. Luis Castelazo Ayala, Mexican Social Security Institute, Magdalena No. 289, Col. Tizapán San Angel, CP 01090, Del. Av. Rio Alvaro Obregon. Mexico DF, Mexico

ARTICLE INFO

Article History:
Received: March 23, 2015
Accepted: May 26, 2015

Corresponding Author:
Maira Huerta-Reyes
Unit of Medical Research in Pharmacology, Specialities Hospital, XXI Century National Medical Center, Mexican Social Security Institute, Av. Cuauhtemoc No. 330, Col. Doctores, Del. Cuauhtémoc, CP 06720, Mexico DF, Mexico

ABSTRACT

Heteropterys is the largest genus in the botanical family Malpighiaceae that comprises more than 140 species. In the last years there has been an increasing interest on *Heteropterys* species because of the promising results of the pharmacological studies that explored *Heteropterys* species for first time. The objective of this review is to provide an overview of the active constituents isolated from *Heteropterys* genus, highlighting the aspects reported on the diversity of the biological activities tested during the past years. For this purpose, we reviewed the scientific literature available for the total number of species that belong to *Heteropterys* in specialized databases. Our findings showed that the properties on CNS (anxiolytic, antidepressant, improving learning and memory), the antioxidant effects and the protective activities of reproductive male organs are the most important biological activities reported for species of *Heteropterys*. Flavonoids are the chemicals most conspicuous, following by aliphatic nitro compounds and hydroxycinnamic acids identified in *Heteropterys*. This review pretend to be helpful for phytochemists and pharmacologist in the proposal of *Heteropterys* as potential source of metabolites that could be used to drug prototypes to many and diverse pathological or physiological situations.

Key words: *Heteropterys*, Malpighiaceae, flavonoids, aliphatic nitro compounds, hydroxycinnamic acids

INTRODUCTION

Malpighiaceae is a family of flowering plants that comprises approximately 75 genera and 1300 species of the tropics and subtropics. About 80% of the genera and 90% of the species occur in the New World (West Indies and the southernmost United States to Argentina) and the rest in the Old World (Africa, Madagascar and Indomalaysia to New Caledonia and the Phillipines) (Anderson *et al*., 2006).

Although, the species belonging to Malpighiaceae family do not have an outstanding economic value, *Malpighia glabra* (Barbados cherry) and *Malpighia emarginata* (Acerola) possess high nutritional value since they are well known as a rich source of vitamin C (Lombello and Forni-Martins, 2003; Nunes *et al*., 2013), while juicy fruits of *Byrsonima* and *Malpighia* are eaten fresh or prepared or canned juices, in jellies, ice cream and preserves that are widely appreciated in the Latin American culinary field (Heywood, 2007). Besides, species of the genera *Acridocarpus*, *Banisteriopsis*, *Byrsonima*, *Galphimia*, *Heteropterys*, *Malpighia*, *Peixotoa* and *Stigmaphyllon* are cultivated as ornamental plants (Lombello and Forni-Martins, 2003; Leon, 2005). In the

evolution field, Malpighiaceae may be considered higher in evolutionary status, because the family has been placed at the ultimate level of evolution in the Hutchinson´s tribal classification (Meeuse, 1986).

On the other hand, some species of the Malpighiaceae have a traditional use, mainly as modulators of CNS. Among them, *Banisteriopsis caapi* stands particularly, since it is the basic ingredient of Ayahuasca, an Amazonian psychoactive beverage of the religious ceremonies that containing the serotonergic 5-HT2A agonist, N, N-dimethyltryptamine (DMT) and the monoamine oxidase-inhibiting alkaloids (harmine, harmaline and tetrahydroharmine) (Bouso *et al*., 2012). In the preparation of Ayahuasca is frequent to found the leaves of other species, namely *Psychotria viridis* (Rubiaceae) (Carlini, 2003) or *Diplopterys cabrerana*, another species of Malpighiaceae (McKenna *et al*., 1984). Hence, the most conspicuous chemical constituents detected in the species belonging to Malpighiaceae are alkaloids-type. However, recent advances showed that other extracts from Malpighiaceae species exhibited a variety of effects, which chemical contents comprise anthocyanins, flavonoids, terpenoids and tannins localized in different genera (De Frias *et al*., 2012; Liu *et al*., 2014; Vendramini and Trugo, 2004).

In spite of *Byrsonima* has been the genus most extensively studied in Malpighiaceae family, because its traditional uses and its number of species (Guilhon-Simplicio and Pereira, 2011), at moment *Heteropterys* is considered as the largest genus in the family with more than 140 species that thrive in diverse habitats, from savannas and dry woodlands to rain forests, in the New World tropics and subtropics from northern Mexico and the West Indies to northern Argentina and southeastern Brazil (Anderson *et al*., 2006; Davis and Anderson, 2010). The genus *Heteropterys* is defined by its samaras, which are unique in the family. In most genera of Malpighiaceae, samaras have a dominant dorsal wing that is thickened along the upper (adaxial) margin and the parallel veins bend downward, ending in the thinner abaxial margin. In *Heteropterys* that situation is reversed, because the adaxial margin of the samara is thinner than the abaxial margin and the wing bends more or less upward with the veins following that curvature (Anderson *et al*., 2006).

In the last years there has been an increasing interest on *Heteropterys* species because of the promising results of the pharmacological studies that explored *Heteropterys* species for first time. Due to such pharmacological potential, the objective of this review is to provide an overview of the extracts and active constituents isolated from *Heteropterys* genus, highlighting the aspects reported on the diversity of the biological activities tested during the past years.

Current taxonomic status of the Genus *Heteropterys*: As we pointed before, although *Heteropterys* is considered as the largest genus in the family with more than 140 species, nowadays some scientific names of its species are still undetermined taxonomically. Because of the contemporary biomedical studies demands a rigorous assessment of the taxonomic nomenclature as a core part of the research in plants (Rivera *et al*., 2014), we reviewed the most accepted international data bases of taxonomic nomenclature, such as TROPICOS (TR) (Tropicos, 2015), The Plant List (TPL) (TPL, 2013) and the International Plant Names Index (IPNI) due to the veracity of their contents (Rivera *et al*., 2014; Bennett and Balick, 2014) and also in order to conform an exhaustive list of the species belonging to genus *Heteropterys*. All names were corrected with based on the database "Nomenclature for Malpighiaceae" by Anderson *et al*. (2006) since this database comprises extensive information on all validly published names for taxa of New World Malpighiaceae and many taxa of Old World Malpighiaceae and is maintained and actualized by taxonomist experts on Malpighiaceae family (Anderson *et al*., 2006). The results of this search are shown in Table 1.

Chemical-pharmacological studies of the species belonging to genus *Heteropterys*: Besides of the studies that focused on the taxonomy, ecology, evolution and ethnobotany, *Heteropterys* genus has been also screened for several trials. Based on the Table 1, we reviewed the pharmacological and phytochemistry reports from the total of the 145 species of *Heteropterys* and the reports found are showing below.

***Heteropterys angustifolia*:** A screening study for detection and identification of the aliphatic nitro compounds as highly poisonous constituents from plant species was conducted in 124 species from 98 genera and 46 families. A single species, *H. angustifolia* was found to contain hiptagin (1, 2, 4, 6-tetra-3-nitropropanoyl-β-D-glucopyranoside). The fresh roots gave a very strong positive test while the fresh aerial parts showed a weakly positive. In contrast, the heat-dried samples exhibited a weak or negative test (Stermitz *et al*., 1975).

***Heteropterys brachiata*:** Based on the traditional medicinal applications of *H. brachiata* in nervous disorders, a study of the neuropharmacological activities of the methanolic extract of the aerial parts of *H. brachiata* at doses of 500, 750, 1000 and 1500 mg kg^{-1} was performed on ICR mice. In the forced swimming test, the extract produced a significant antidepressant effect at doses of 500 and 750 mg kg^{-1}. A clear dose-dependent anxiolytic activity was exhibited by methanolic extract in the elevated plus maze model by doses from 500-1500 mg kg^{-1}. In the same work, a significant anticonvulsant activity in the pentylenetetrazole-induced seizures test was observed at dose of 500 mg kg^{-1} and no sedation effects were detected after the administration of sodium pentobarbital in mice. In the acute toxicity test, the extract could be considered as safe, since no deaths were observed in mice treated orally with 2000 mg kg^{-1}. The HPLC analysis of the methanolic extract of *H. brachiata* active as antidepressant, anxiolytic and anticonvulsant revealed that the main compounds present in the extract were chlorogenic acid (3.2 mg kg^{-1}) and chlorogenic acid methyl ester (60 mg kg^{-1}). It was possible also detected the presence of a complex

Table 1: Species of the genus *Heteropterys* (Malpighiaceae)

Scientific name	Data base	Synonyms
H. actinotecnia W.R. Anderson	TR, TPL, IPNI	
H. admirabilis Amorim	TR, TPL, IPNI	
H. aenea Griseb.	TR, TPL, IPNI	
H. aequatorialis W.R. Anderson	TR, TPL, IPNI	
H. alata (W.R. Anderson) W.R. Anderson	TR, TPL, IPNI	
H. aliciae W.R. Anderson	TR, TPL, IPNI	
H. alternifolia W.R. Anderson	TR, TPL, IPNI	
H. amplexicaulis Morong	TR, TPL, IPNI	
H. andersonii Amorim	TPL, IPNI	
H. andina Amorim	TR, TPL, IPNI	
H. arenaria Markgr.	TR, TPL, IPNI	
H. argyrophaea A. Juss.	TR, TPL, IPNI	
H. atabapensis W.R. Anderson	TR, TPL, IPNI	
H. aureosericea Cuatrec.	TR, TPL, IPNI	
H. ayacuchensis W.R. Anderson	TR, TPL	
H. bahiensis Nied.	TR, TPL, IPNI	
H. banksiifolia Griseb.	IPNI, TPL	*H. brasiliensis* Regel and Körn
H. berteroana Adr. Juss.	TR, IPNI	*H. formosa* C.V. Morton and Cuatrec
H. bicolor A. Juss.	TR, TPL, IPNI	
H. biglandulosa A. Juss.	TR, TPL	
H. brachiata (L.) DC.	TR, TPL, IPNI	*H. beecheyana* A.Juss *H. retusa* Donn. Sm *H. simulans* (Small) Nied
H. brunnea R. Sebast. and Mamede	IPNI, TPL	
H. bullata Amorim	TR, TPL, IPNI	
H. buricana Cuatrec. and Croat	TR, TPL, IPNI	
H. byrsonimifolia A. Juss.	TR, TPL, IPNI	
H. caducibracteata W.R. Anderson	TR, TPL, IPNI	
H. campestris A. Juss.	IPNI	*H. confertiflora* A. Juss. *H. discolor* A. Juss.
H. capixaba Amorim	TR, TPL, IPNI	
H. catingarum A. Juss.	TR, TPL, IPNI	
H. chrysophylla (Lamb) DC.	TR, TPL, IPNI	*H. chrysophylla* Kunth
H. ciliata Nied.	TR, TPL, IPNI	
H. cochleosperma A. Juss.	TR, IPNI	*H. hassleriana* Nied.
H. coleoptera A. Juss.	TR, TPL, IPNI	*H. metallochroa* A. Juss.
H. colombiana W.R. Anderson	TR, TPL, IPNI	
H. complicata (Kunth) W.R. Anderson and C. Davis	TR, TPL, IPNI	
H. conformis W.R. Anderson	TR, TPL, IPNI	
H. cordifolia A. Juss.	TR, TPL, IPNI	*H. cordifolia* Moric.
H. coriacea A. Juss.	TR, TPL, IPNI	
H. corumbensis Kuntze	TR, TPL, IPNI	
H. cotinifolia A. Juss	TR, IPNI	*H. arborescens* Brandegee. *H. pallida* Brandegee *H. gayana* A. Juss. *H. portillana* S. Watson
H. crinigera Griseb.	TR, TPL, IPNI	
H. cristata Benth.	TR, IPNI	*H. carinata* Benth.
H. cuatrecasasii W.R. Anderson	TR, TPL, IPNI	
H. cultriformis Chodat	TR, TPL, IPNI	
H. dichromocalyx W.R. Anderson	TR, TPL, IPNI	
H. duarteana A. Juss.	TPL, IPNI	*H. xanthophylla* A. Juss.
H. dumetorum (Griseb.) Nied.	TR, IPNI	*H. paraguariensis* Nied. *H. praecox* Nied.
H. dusenii Nied.	TR, TPL, IPNI	
H. eglandulosa A. Juss.	TR, IPNI	*H. anoptera* A. Juss.
H. escalloniifolia A. Juss.	TR, TPL , IPNI	*H. affinis* A. Juss.
H. falcifera A. Juss.	TR, TPL	
H. floridana Cuatrec.	TR, TPL, IPNI	
H. fluminensis (Griseb.) W.R. Anderson	TR, TPL, IPNI	
H. fruticosa W.R. Anderson	TR, TPL, IPNI	
H. fulva Cuatrec.	TR, TPL, IPNI	
H. gentlei Lundell	TR, TPL, IPNI	
H. glabra Hook. and Arn.	TR, IPNI	*H. angustifolia* Griseb. *H. charruarum* Herter *H. lanceolata* (Nied.) Herter *H. pseudoangustifolia* Chodat

Table 1: Continue

Scientific name	Data base	Synonyms
H. glazioviana Nied.	TPL, IPNI	
H. grandiflora A. Juss.	TR, TPL, IPNI	
H. guianensis W.R. Anderson	TR, TPL, IPNI	
H. hammelii W.R. Anderson	TR, TPL, IPNI	
H. hatschbachii W.R. Anderson	TR, TPL, IPNI	
H. hoffmanii W.R. Anderson	TR, TPL, IPNI	
H. huberi W.R. Anderson	TR, TPL, IPNI	
H. hypericifolia A. Juss.	TR, TPL, IPNI	
H. imperata Amorim	TR, TPL, IPNI	
H. intermedia (A. Juss.) Griseb.	TR, TPL, IPNI	*H. aceroides* Griseb. *H. diversifolia* A. Juss. *H. hiraeoides* A. Juss. *H. venosa* Griseb.
H. jardimii Amorim	TPL, IPNI	
H. krapovickasii W.R. Anderson	TR, TPL, IPNI	
H. laurifolia (L.) A. Juss.	TR, IPNI	*H. caerulea* (Lam.) DC. *H. floribunda* Kunth *H. longifolia* Kunth
H. leona (Cav.) Exell	IPNI	*H. africana* A. Juss. *H. jussieui* Hook. f.
H. leschenaultiana A. Juss.	TR, TPL, IPNI	
H. lindeniana A. Juss.	TR, IPNI	*H. heterocarpa* (Standl.) Standl.
H. lindleyana A. Juss.	TR, TPL, IPNI	*H. transiens* Nied.
H. lonicerifolia Triana and Planch.	TR, TPL, IPNI	
H. machaedophora Nied.	TR, IPNI	
H. macradena (DC.) W.R. Anderson	TR, TPL, IPNI	*H. candolleana* A. Juss. *H. lessertiana* A. Juss.
H. macrostachya A. Juss.	TR, TPL, IPNI	*H. apiculata* Miq. *H. aureonitens* Planch. and Linden *H. belizensis* Lundell
H. magnifica W.R. Anderson	TR, TPL, IPNI	
H. maguirei W.R. Anderson	TR, TPL, IPNI	
H. marginata W.R. Anderson	TR, TPL, IPNI	
H. marleneae W.R. Anderson	TR, TPL, IPNI	
H. mathewsiana A. Juss.	TR, TPL, IPNI	
H. megaptera A. Juss.	TPL, IPNI	*H. lasseri* W.R. Anderson
H. minutiflora Amorim	TR, TPL, IPNI	
H. molesta W.R. Anderson	TR, TPL, IPNI	
H. mollis Nied.	TR, TPL, IPNI	
H. mulgurae W.R. Anderson	TR, TPL, IPNI	
H. murcapiresii W.R. Anderson	TR, TPL, IPNI	
H. neblinensis W.R. Anderson	TR, TPL, IPNI	
H. nervosa A. Juss.	TR, IPNI	*H. mossii* (C.V. Morton) Cuatrec. *H. suberosa* Griseb.
H. nitida (Lam.) DC.	TR, TPL, IPNI	
H. nordestina Amorim	TR, TPL, IPNI	
H. oberdanii Amorim	TR, TPL, IPNI	
H. oblongifolia Gleason	TR, TPL, IPNI	
H. obovata (Small) Cuatrec. and Croat	TR, IPNI	*H. petenensis* Lundell
H. occhionii Amorim	TPL, IPNI	
H. occidentalis Cuatrec.	TR, IPNI	
H. oligantha W.R. Anderson	TR, TPL, IPNI	
H. olivacea (Cuatrec.) W.R. Anderson	TR, TPL, IPNI	
H. orinocensis (H. B. K.) Adr. Juss.	TR, IPNI	*H. acutifolia* A. Juss., *NON H. acutifolia* Arech. *H. helicina* Griseb.
H. ovalifolia Rusby	TR, IPNI	
H. ovata (Nied.) W.R. Anderson and C. Davis	TR, IPNI	
H. oxenderi W.R. Anderson	TR, TPL, IPNI	
H. palmeri Rose	TR, TPL, IPNI	
H. panamensis Cuatrec. and Croat	TR, TPL, IPNI	
H. pannosa Griseb.	TR, TPL, IPNI	
H. patens (Griseb.) A. Juss.	TR, TPL, IPNI	*H. anomala* A. Juss.
H. pauciflora A. Juss.	TR, TPL, IPNI	
H. perplexa W.R. Anderson	TR, TPL, IPNI	
H. platyptera DC.	TR, TPL, IPNI	
H. prancei W.R. Anderson	TR, TPL, IPNI	
H. procoriacea Nied.	TR, TPL, IPNI	
H. prunifolia (Kunth) W.R. Anderson	TR, TPL, IPNI	*H. rhombifolia* A. Juss.

Table 1: Continue

Scientific name	Data base	Synonyms
		H. venezolensis Nied.
H. pteropetala A. Juss.	TR, TPL, IPNI	
H. purpurea (L.) Kunth	TR, TPL, IPNI	*H. parvifolia* (Vent.) DC.
H. quetepensis Steyerm.	TR, TPL, IPNI	
H. racemosa A. Juss.	TR, IPNI	
H. reticulata Griseb.	TPL, IPNI	*H. grisebachiana* Nied.
H. rhopalifolia A. Juss.	TR, TPL, IPNI	
H. riparia Cuatrec.	TR, TPL, IPNI	
H. rubiginosa A. Juss.	TPL, IPNI	*H. chodatiana* Skottsb.
H. rudasii W.R. Anderson	TR, IPNI	
H. rufula A. Juss.	TR, TPL, IPNI	
H. sanctorum W.R. Anderson	TR, TPL, IPNI	
H. schulziana W.R. Anderson	TR, TPL, IPNI	
H. sericea (Cav.) A. Juss.	TR, TPL , IPNI	
H. sessilifolia A. Juss.	TR, TPL, IPNI	
H. siderosa Cuatrec.	TR, TPL, IPNI	
H. sincorensis W.R. Anderson	TR, TPL, IPNI	
H. spiraeae Mart. ex. A. Juss	IPNI	
H. standleyana W.R. Anderson	TR, TPL, IPNI	
H. steyermarkii W.R. Anderson	TR, TPL, IPNI	
H. subhelicina Nied.	TR, TPL, IPNI	*H. catoptera* W.R. Anderson
H. sylvatica A. Juss.	TR, IPNI	*H. tenuifolia* (Nied.) Nied.
H. syringifolia Griseb.	TR, IPNI	*H. australis* A. Juss.
		H. martiana A. Juss.
H. ternstroemiifolia A. Juss.	TR, TPL, IPNI	
H. thyrsoidea A. Juss.	TR, TPL, IPNI	
H. tomentosa Adr. Juss.	TR, IPNI	*H. aphrodisiaca* Machado
		H. nudicaulis S. Moore
		H. ocellata L.B. Sm.
		H. spectabilis A. Juss.
		H. verbascifolia Griseb.
H. trichanthera A. Juss.	TPL, IPNI	*H. gardneriana* Nied.
H. trigoniifolia A. Juss.	TR, TPL, IPNI	
H. umbellata A. Juss.	TR, TPL, IPNI	*H. anceps* Nied.
		H. regnelli Miq.
H. uribei Cuatrec.	TR, TPL, IPNI	
H. velutina W.R. Anderson	TR, TPL, IPNI	
H. wydleriana A. Juss.	TR, IPNI	*H. bellonis* Urb.

mixture of terpene-type compounds in the active extracts due their retention times and UV absorption (Huerta-Reyes *et al*., 2013a).

***Heteropterys byrsonimifolia*:** A screening against ochratoxin A produced by the fungus *Aspergillus ochraceus* was performed since they are the contaminants of coffee beans, a crop with high commercial value. Among the 43 plants species evaluated, the extract from the leaves of *H. byrsonimifolia* was the most active. Four flavonoids were isolated of *H. byrsonimifolia* active extract, from which rutin exhibited the most potent antifungal effect with a MIC = 32.5 μg mL^{-1}. The study *in silico* revealed that rutin may act against this fungus by binding to a protein kinase. The remain three flavonoids purified from the *H. byrsonimifolia* extract, guaijaverin, quercetin 3-O-α-L-rhamnopyranoside and quercetin 3-O-robinobioside did not exerted inhibitory properties against *A. ochraceus* (Junior *et al*., 2014).

***Heteropterys cotinifolia*:** The endemic species of Mexico *H. cotinifolia* has been used in traditional Mexican medicine mainly for the treatment of nervous disorders. The first study for evaluating the neuropharmacological properties of this species revealed that the methanolic extract produces a dose-dependent antidepressant effect in the forced swimming test at doses from 31-310 mg kg^{-1} when orally administered to ICR mice, without reduction of mice locomotion. In contrast, no anxiolytic effect was observed at those doses in elevated plus maze test. In the active extract, the chlorogenic acid (36.4 mg kg^{-1}) and the flavonoid rutin (17.9 mg kg^{-1}) were identified as main compounds and they may be involved in the antidepressant effects (Huerta-Reyes *et al*., 2013b).

***Heteropterys chrysophylla*:** In the screening of Brazilian plants for antimicrobial (against *Escherichia coli*), antifungal (against *Candida albicans*, *Cladosporium sphaerospermum* and *Cladosporium cladosporioides*) and DNA-damaging activities, the species *H. chrysophylla* was evaluated. However, no activity was shown in any of the assays (Agripino *et al*., 2004). In a different work, the effects on cell proliferation assay of the two prostate cancer cell lines LNCaP and PC-3 were performed in order to detect simultaneous hormonal and cytotoxic effects of plant extracts or compound mixtures. The extract of leaves and twigs of *H. chrysophylla* exhibited hormonal influences on prostate cancer cells since the extract stimulated the proliferation of LNCaP cells without

having a proliferation stimulating activity on PC-3 cells. The phytochemical investigation reveals the presence of two flavonol glycosides kaempferol-3-O-α-L-rhamnoside and kaempferol-3-O-α-L-rhamnose-(2→1)-β-D-xylopyranoside (Bobach *et al*., 2014).

***Heteropterys glabra*:** In order to validate the use in the South-American folk medicine of the species *H. glabra* as sedative and anxiolytic agent, the ethanolic extract of fruits from *H. glabra* were evaluated respecting the neurophysiological effects in DBA/2J mice. The sleep wakefulness cycle, the electroencephalogram and visual evoked potentials were the parameters evaluated at 35, 350 and 700 mg kg^{-1} doses. Since, the oral administration of the *H. glabra* extract exhibited a reduction of motor activity together with the alterations of electroencephalogram parameters in mice, *H. glabra* possesses anxiolytic/sedative properties, confirming their traditional use (Galietta *et al*., 2005).

***Heteropterys tomentosa*:** The roots of *H. tomentosa* are used as aphrodisiac, tonic or stimulant, as well as for nervous debility, vasodilatation and antiulcer in Brazil (Galvao *et al*., 2011; Veggi *et al*., 2011). Diverse studies for exploring the possible biological properties, in particular of the extracts of roots of *H. tomentosa*, have been carried out.

A study to evaluate the effects of oral dosing of the standardized extract from the roots of *H. tomentosa* (called BST0298) was realized in 2002. In that investigation, treatments for 7 days (50 mg kg^{-1}) or 26 days (100 mg kg^{-1}) had a positive effect on memory in aged rats and in the T-maze left/right discrimination test. However, the administration of acute treatment (100 mg kg^{-1}) not showed effects on improvement on memory in aged rats (Galvao *et al*., 2002). In the same contribution, a preliminary qualitative phytochemical analysis revealed that the standardized extract BST0298 contents flavonoid glycosides, cardiac glycosides with steroidal nucleus, aromatic glycosides, cardiac glycosides with pentagonal lactonic ring, saponins, hydrolyzable and condensed tannins and aliphatic nitro compounds (Galvao *et al*., 2002). Further studies, revealed that the standardized extract BST0298 of *H. tomentosa* was effective in improving the memory of aged animals in a T-maze after repeated administration of small doses (25 or 50 mg kg^{-1}), but had no effect on the scopolamine-induced amnesia test. These results suggest that repeated treatment with *H. tomentosa* improves learning and memory by a non-muscarinic mechanism. The phytochemical characterization of the BST0298 extract showed the presence of the flavonoids astilbin, neoastilbin and isoastilbin, as well as an aliphatic nitro compound identified as 2, 3, 4, 6-tetra-O-(3-nitropropanoyl)-O-β-D-glucopyranoside. Moreover, the BST0298 extract presented marked antioxidant activity by inhibition of lipid peroxidation, which can contribute for beneficial effect on memory (Galvao *et al*., 2011).

Concerning the studies that focused on verify the adaptogenic potential of the hydroalcoholic extract of *H. tomentosa*, a couple of contributions can be found in literature. An evaluation of some stress response parameters after 7 days treatment at doses of 100 and 300 mg kg^{-1} was performed. It also included the evaluation of learning and memory of aged rats treated at the dose of 50 mg kg^{-1} for 80 days in the elevated T-maze test. As results, any of the extracts tested from the roots, branches and leaves of *H. tomentosa* were capable of protecting the stomach from ulcerations, nor protecting from alterations in adrenal or spleen weight, not inhibited increases in plasma levels of corticosterone and adrenocorticotropic hormone. Also the extracts from *H. tomentosa* did not inhibit self-analgesia induced by restraint stress and did not improve the performance of aged rats in the T-maze test. The chemical constituents of the extracts from the three different plant organs of *H. tomentosa* did not present conclusive differences (Paula-Freire *et al*., 2013). The second contribution for the adaptogenic effect determined the protective effect on cell death by apoptosis, using the TUNEL technique for measuring the percentage of apoptosis in the hippocampus of male Wistar rats treated orally for 30 d with doses of 50 mg kg^{-1} of the *H. tomentosa* extract. However, no differences in the percentage of apoptosis in the hippocampus of aged rats were found (Bezerra *et al*., 2013).

Since the medicinal properties of *H. tomentosa* could at least partially be explained by a possible antioxidant activity (Leite *et al*., 2012), some studies have been interested in evaluate the antioxidant properties of the extract of the roots. An outstanding antioxidant activity of the ethanolic extract of *H. tomentosa* (5452±72 μmol TE g^{-1} dw) was observed by ORAC assay (oxygen radical absorbance assay), using the AAPH reactive species, a peroxyl radical generator (ROO). This antioxidant activity contrast with several other folk medicinal, plants that known for their potent antioxidant properties such as aqueous extract of green tea (814±30 μmol TE g^{-1} dw) and aqueous extract of black tea (927 μmol TE g^{-1} dw) (Leite *et al*., 2012). Other report referred that a chronic treatment in young and old rats with 50 mg kg^{-1} showed an increase in the Superoxide Dismutase (SOD) activities (40%) in the brain of old rats but no changes were detected in catalase and Glutathione Peroxidase (GPX). In the case of young rats, no significant variations in antioxidant enzyme were detected. However, lower levels of lipoperoxidation (30%) detected in the brain of young rats after the administration of the extract of *H. tomentosa* suggested that this plant reduce the oxidative stress to brain lipids (Mattei *et al*., 2001). In the area of study of foods and nutraceuticals, because of the well-known antioxidant properties of the phenolic compounds, there is a particular interest for applications in these areas of the plant species reported with high antioxidant properties (Scalbert *et al*., 2005; Veggi *et al*., 2011). Hence, the extract of *H. tomentosa* was subject of evaluation for the quality of production and for economical evaluation of the supercritical fluid extraction method. The aqueous extract obtained of *H. tomentosa* resulted as the most viable commercial extract among the 5 selected species investigated due to its high phenolic content and low cost of production (Veggi *et al*., 2011).

Based on the traditional use of *H. tomentosa* as aphrodisiac, some studies had been conducted in order to evaluate the possible stimulant/protective effects of *H. tomentosa* extracts on male reproductive structures. The administration of the aqueous extract of *H. tomentosa* on rats showed the protective effect of the extract on the testis ultrastructure by reducing the CsA-induced damage (Monteiro *et al*., 2008). In the case of prostate tissue, the administration of the infusion of *H. tomentosa* showed to be efficient against the side effects of the long term intake of CsA observed by plasmic biochemical parameters and without toxicity signs (Freitas *et al*., 2013). Other contribution exhibited the capacity of the *H. tomentosa* for increasing the spermatogenic yield by the increasing of the testosterone production and the spermatogonia mitosis in testes of adult Wistar rats (Gomes *et al*., 2011).

On the other hand, the effects of the infusion of *H. tomentosa* were investigated on tendon properties under long term endurance training. The results reveled that *H. tomentosa* increased the collagen molecules and the corresponding organizational increase resulted in more resistant tendons (Monteiro *et al*., 2011).

As we mentioned before, aliphatic nitro compounds have been isolated from *Heteropterys* species. In the case of *H. tomentosa*, the compound 2, 3, 4, 6-tetra-O-(3-nitropropanoyl)-O-β-D-glucopyranoside isolated from the roots, was tested for antimicrobial, antifungal and antiviral properties. For antimicrobial activities the compound was tested against *Bacillus subtilis* and *Staphylococcus aureus* and the values calculated for the minimal inhibitory concentration (MIC) were 250 and 500 μg mL^{-1}, respectively. The antifungal activity was stronger than antibacterial, where the Minimal Fungicidal Concentration (MFC) was 250 μg mL^{-1} for each species of *Candida*: *C. albicans*, *C. parapsilosis*, *C. krusei* and *C. tropicalis* (Junior *et al*., 2005). The antiviral effects were tested against Poliovirus type 1 (PV-1) and bovine herpes virus type 1 (BHV-1), where the compound exhibited a moderate antiviral activity with an IC_{50} = 22.01 μg mL^{-1} (selectivity index = 2.83) and 21.10 μg mL^{-1} (selectivity index = 2.95), respectively (Melo *et al*., 2008).

A pharmacognostic analysis of the roots of *H. tomentosa* revealed that the values for physic-chemical parameters could be helpful in the identification and the optimum moment of the plant for drug purposes: total phenol content rise its higher value in spring (10.2%) suggesting this season as the most appropriate for harvest the plant drug, while the flavonoids neoastilbin, astilbin and isoastilbin detected by HPLC may be used as markers and therefore, as auxiliary in the identification of the plant species (Marques *et al*., 2007).

DISCUSSION

The majority of the pharmacological literature reviewed here, showed that the neuroproperties are the bioactivities most studied in species from *Heteropterys* genus, following by antioxidant properties. Interestingly, mostly of these investigations that evaluated CNS activities comprise standardized extracts that partially reveal the chemical composition of the active extract: methanolic extract with presence of chlorogenic acid, chlorogenic acid methyl ester, and triterpene-type compounds in the case of *H. brachiata* for example (Huerta-Reyes *et al*., 2013a). In contrast, curiously the investigations that reveal the characterization of pure compounds obtained from extracts of the species of *Heteropterys* genus did not examined properties related with CNS but focused on other biological activities, such as antifungal, antimicrobial or antiviral (Junior *et al*., 2005; Melo *et al*., 2008). In this manner, the information of the pure compounds obtained from *Heteropterys* genus that possess CNS effects is still scarce.

On the other hand, *H. tomentosa* is the species with the greatest number and variety of bioactivities reported among the *Heteropterys* species. Probably, this may be due to the species *H. aphrodisiaca* are currently considers by botanists as a synonym of *H. tomentosa* (Araujo *et al*., 2010) and a plant that is widely used by population in Brazil (Paula-Freire *et al*., 2013) that even some commercial products are available in the market. Due its value, scientific literature reveals an interest to explore the possible effects of the extracts of the roots of *H. aphrodisiaca* on CNS, considering that more recent investigations made reference to the accepted scientific name *H. tomentosa*. However, additional to affections on CNS, the antioxidant, protective action on prostate, antimicrobial, antifungal, increasing the spermatogenic yield and strengthening of tendons are the properties also evaluated scientifically for *H. tomentosa* extracts. As result, only some flavonoids, such as neoastilbin, astilbin and isoastilbin (Marques *et al*., 2007) and a nitro-compound [2,3,4,6-tetra-O-(3-nitropropanoyl)-O-β-D-glucopyranoside] (Junior *et al*., 2005; Melo *et al*., 2008) have been identified as chemicals present in the extracts from the roots of *H. tomentosa*, while the majority of these investigations comprise crude extracts.

In addition to the effects on CNS and antioxidant properties mentioned above, the effects on male reproductive structures by the extracts of *Heteropterys* species are the third in importance. However, from these studies only two flavonoids were identified in *H. crysophylla*: kaempferol-3-O-α-L-rhamnoside, and kaempferol-3-*O*-α-L-rhamnose-(2→1)-β-D-xylopyranoside (Bobach *et al*., 2014). In consequence and to the best of our knowledge, from the total of molecules identified in the extracts from the *Heteropterys* genus, flavonoids are the most conspicuous, following by aliphatic nitro compounds and hydroxycinnamic acids.

In this contribution we reviewed the phytochemical and the pharmacological information considering the total of the 145 species of *Heteropterys* genus. However, to the best of our knowledge, these phytochemical and pharmacological information is available only for <5% of the total of the valid species from the genus (Table 1). Hence, *Heteropterys* seems as an attractive subject the study as a potential source of metabolites that could be used to drug prototypes. Future contributions about the chemical contents of *Heteropterys* may be reveal new structural molecules and more bioactive constituents.

CONCLUSION

Although, species of plants that belong to *Heteropterys* genus have been investigated with intensity on last decade, the characterization of chemical active composition from the active extracts as therapeutic agents are still ongoing. The diverse biological activities including effects on CNS, the antioxidant, protective action on prostate, antimicrobial, antifungal, increasing the spermatogenic yield and strengthening of tendons, reveals a growing interest from researchers in the study of the genus. Since approximately only <5% of the species of *Heteropterys* have been studied from the pharmacological and/or chemical perspective, this review pretend to be helpful for phytochemists and pharmacologist in the proposal of *Heteropterys* as potential source of metabolites that could be used to drug prototypes to many and diverse pathological or physiological situations.

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