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Genus *Mikania*: chemical composition and phytotherapeutical activity

Luciane C. Rufatto,[1] Adriana Gower,[2] Joséli Schwambach,[1] Sidnei Moura[1,2]

[1]Instituto de Biotecnologia, Universidade de Caxias do Sul, Brazil,
[2]Centro Tecnológico, Universidade de Caxias do Sul, Brazil.

Review

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Abstract: The genus *Mikania* ranks high in the list of best-selling natural products in the world. Its main distribution is in South America, but some species are found in Asia, North America and Africa. It is used for treating fever, rheumatism, colds and respiratory diseases, as well as snake bites and scorpion stings, due to its broad spectrum of action. There are approximately 430 species of this genus and only 12% have been studied, highlighting their chemical and pharmacological diversity. The main chemical groups are: coumarins and derivatives, sesquiterpenes, sesquiterpenes lactones, diterpenes, phytosterols/terpenoids and flavonoids. This review aims to supply useful references for scientists interested in natural products and the search for new compounds, from over the 300 already described for the genus.

Introduction

For centuries, many medicinal plants have been used all over the world as a sort of treatment of various diseases through yet unknown mechanisms. The number of herbal medicines has increased every year, and the phytotherapic market trades billions of dollars annually (Marcus & Grollman, 2002). Moreover, most compounds present in plants may cause serious side effects. Hence, the correct identification and separation of chemical structures of the major components is crucial, making the use of active medicinal plants safe.

The genus *Mikania* is the largest of its kind in the Eupatorieae (Asteraceae) tribe, with more than 430 species concentrated mainly in the tropical regions (King & Robinson, 1987). Although it is one of the most distinctive and easily recognized genera of the tribe, species delimitation is often difficult due to the very large number of taxa and the existence of highly polymorphic species complexes (King & Robinson, 1987). In Brazil, the genus with 171 species is mainly found in the states of São Paulo, Minas Gerais and Rio de Janeiro (Gasparetto et al., 2010). The species of this genus are characterized by herbaceous, annual or perennial (Pio Correa, 1984), and scandent habit, though there are as well commonly erect and decumbent representatives (Ritter & Miotto, 2005). Some species known as "guaco" have shown a broad spectrum of action and are used to treat fever, rheumatism, colds and respiratory diseases (Silva et al., 1984; Moura et al., 2002; Oliveira et al., 2007; Soares et al., 2007; Freitas et al., 2008). Approximately 12% of *Mikania* species and their chemical composition have been studied. The most commonly used are *Mikania glomerata* and *Mikania laevigata*, generally employed in respiratory disorders treatments (Gasparetto et al., 2010), and because their morphological and anatomic similarities are sold indiscriminately and used without distinction (Ritter & Miotto, 2005; Bolina et al., 2009). However, other species are described in the literature, and are characterized for their chemical components activities. This review aims to identify key species, their chemical components and the main herbal medicine action reported as a guide to future research on the *Mikania* genus.

Chemical composition

Different classes of compounds were previously isolated from various *Mikania* parts, which can be associated to this plant's pharmacological activities. The main groups are: coumarins and derivatives, sesquiterpenes, sesquiterpenes lactones, diterpenes, phytosterols/terpenoids and flavonoids. Caffeoylquinic acid derivatives beyond others chemical compounds are found in smaller amount. Diterpenes such as kaurenoic acid and benzoylgrandifloric acid (class of kauranes), have also attracted interest for their pharmacological action. Moreover, detailed screenings revealed the presence of other substances in species of *Mikania* as

alcohols, acids, esters, aldehydes and organic esters (Gasparetto et al., 2010).

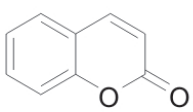
Coumarins and derivatives

The most characteristic class of compounds in *Mikania* genus are the coumarins and derivatives, frequently responsible for pharmacological activity. A wide variety of biological activities is assigned for these compounds, such as antimicrobial, antiviral, anti-inflammatory, antispasmodic, antitumoral, anticoagulant, bronchodilator and antioxidant (Pereira et al., 1992; Hoult & Payá, 1996). The coumarin (1,2-benzopyran) (**1**), dihydrocoumarin and *o*-coumaric acid were identified in extracts of *M. glomerata* (Vidal et al., 2006) and *M. laevigata* (Oliveira et al., 1984). Herz & Kulanthaivel (1985) discovered in *M. congesta* aerial parts, growing in the state of Pará-Brazil, some similar compounds such as scopoletin (**2**), *O*-geranylscopoletin. In *M. shushunensis*, collected in Peru, herniarin (7-methoxycoumarin) (**3**) and 2,6-dimethoxyquinone (Gutierrez & Herz, 1988) has been described.

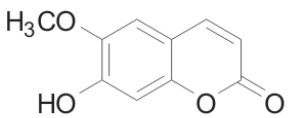
Sesquiterpenes and terpenes, diterpenes and sesquiterpenes lactones

Sesquiterpenes are abundant in *Mikania* genus, related to that the most commom are germacrene D, isocomene and γ-humulene. These compounds were reported in around 15% of *Mikania* species that already had their chemical composition determined, among them *M. arrojadoi* (Bohlmann et al., 1982b), *M. officinalis*, *M. sessilifolia*, *M. luetzelburgii* and *M. belemii* (Bohlmann et al., 1981). Chart 1 presents in detail the species studied and the compounds that have been described.

Likewise, terpenes, diterpenes and sesquiterpene lactones are often found, mainly the dilactones type mikanolide and miscandenin derivatives, which have analgesic activity (Ahmed et al., 2001), antibacterial (Facey et al., 2010) and anti-cancer properties (Prevost et al., 2002). A list of species and the lactones compounds described for each of them is presented in Chart 2.



1



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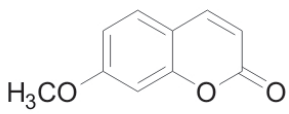


3

Chart 1. Sesquiterpenes in *Mikania* genus.

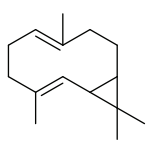
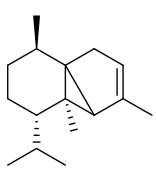
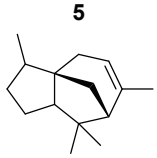
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. laevigata	From São Paulo to Rio Grande do Sul, Brazil	leaves	caryophyllene, bicyclogermacrene (**4**)	 **4**	Limberger et al., 1998
M. cordata	Asia	leaves	α-cubebene (21.3%) (**5**), caryophyllene oxide (10.1%), α-bisabolol (6.6%), γ-curcumene (6.3%), β-pinene (4.1%), copaene (4.1%), α-cedrene (4.9%) (**6**), spathulenol (3%)	 **5**  **6**	Chowdhury et al., 2007

Chart 1. Sesquiterpenes in *Mikania* genus. (cont)

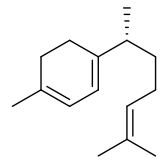
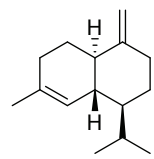
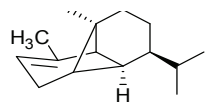
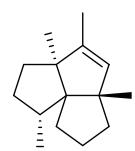
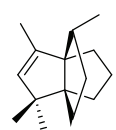
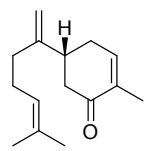
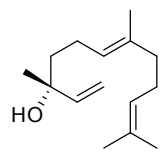
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. cordata	Asia	flowers oil	β-pinene (14.9%), α-cubebene (12.4%), γ-curcumene (11.7%) (**7**), caryophyllene (8.5%), α-bergamotene (5.6%), β-caryophyllene(4.3%), zingiberene (6%)	 **7**	Chowdhury et al., 2007
M. micrantha	Central and South America and widespread in all regions of Asia-Pacific	aerial parts	2-cubebene, γ-elemene, 2-copaene, β-caryophylene, germacrene-D, δ-cadinene (**8**)	 **8**	Nicollier and Thompson, 1981.
M. grazielae	Northeastern Brazil	aerial parts	α-copaene (**9**), longifolene, caryophyllene, α-humulene	 **9**	Bohlmann et al., 1982b
M. goyazensis	Northeastern Brazil	roots and aerial parts	thymol derivatives, isocomene (**10**), β-isocomene, modhephene, phytol, geranylnerol	 **10**	Bohlmann et al., 1982a
M. arrojadoi	Northeastern Brazil	roots and aerial parts	isocomene, β-isocomene, modhephene (**11**), *ent*-kaurene	 **11**	Bohlmann et al., 1982b
M. shushunensis	Province of Loreto, Peru	aerial parts	(-)-cryptomerion (**12**) and its derivatives: (-)-(6R)-10-hydroxybisabol-2,7(14),11-trien-4-one, (-)-(6R)-11-hydroxybisabol-2,7(14)-dien-4-one, (-)-(6R)-10,11-epoxybisabol-2,7(14)-dien-4-one.	 **12**	Gutierrez and Herz, 1988
M. microptera	Tropical regions of Africa and South America	aerial parts	10,11-dihydro-10,11-dihydroxynerolidol, nerolidol (**13**)	 **13**	Diaz et al., 1992

Chart 1. Sesquiterpenes in *Mikania* genus. (cont)

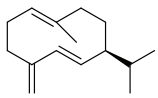
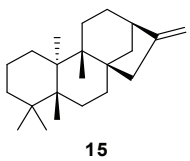
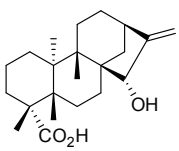
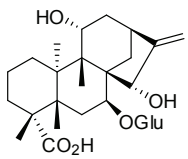
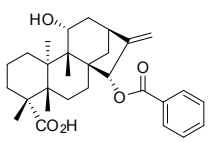
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. purpurascens	Northeastern Brazil	roots and aerial parts	germacrene-D (**14**), 12-hydroxynerolidol	 **14**	Bohlmann et al., 1982b
M. vitifolia	Costa Rica	aerial parts - leaves and stems	kaurene (**15**) derivatives like: *ent*-kaur-16-en-19-oic acid, *ent*-kaur-16-en-19-ol, *ent*-15β-cinnamoyloxy-kaur-16-en-19-oic acid, *ent*-7α-cinnamoyloxy-15β-hydroxy-kaur-16-en-19-oic acid, *ent*-15β-hydroxy-kaur-16-en-19-oic acid (**16**), *ent*-15β-cinnamoyloxy-7α-hydroxy-kaur-16-en-19-oic acid, *ent*-15β-hydroxy-7α-(E)-lachnophylloyloxy-kaur-16-en-19-oic acid	 **15**  **16**	Lobitz et al., 1998
M. hirsutissima	Southwest region of South America	aerial parts	ent-kaurenoic acid derivatives: 2β,16α,17-trihydroxy-ent-kauran-19-oic acid, 3β,16α,17-trihydroxy-ent-kauran-19-oic acid, 11α,15 α-dihydroxy-7-*O*-β-D-glucopyranosyl-ent-kaur-16-en-19-oic acid (**17**), 1α,15β-dihydroxy-7-*O*-β-D-glucopyranosyl-ent-kaur-16-en-19-oic acid	 **17**	Oliveira, 1972; Ohkoshi et al., 2004
M. lindbergii	Brazil, state of Minas Gerais	aerial parts	ent-kaur-16(17)-en-19-oic acid, ent-15β-hidroxykaur-16(17)-en-19-oic acid, ent-16β,17-dihydroxykauran-19-oic acid, ent-17-oxo-kaur-15-en-19-oic acid, ent-15β-benzoyloxykaur-16(17)-en-19-oic acid (**18**), and ent-15β,16β-epoxy-17-hydroxykauran-19-oic acid	 **18**	Fabbri et al. 1997

Chart 2. Sesquiterpenes lactones in *Mikania* genus.

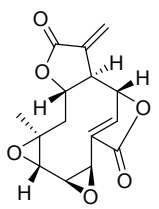
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. scandens	Woods and swamps of the southeastern of United States	aerial parts	mikanolide (**19**), dihydromikanolide, scandenolide, dihydroscandenolide, deoxymikanolide, miscandenin (elemanediolide)	 **19**	Herz et al., 1967; Herz et al., 1970

Chart 2. Sesquiterpenes lactones in *Mikania* genus. (cont)

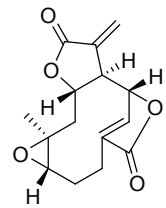
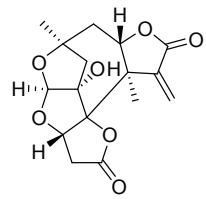
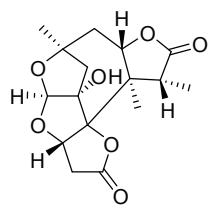
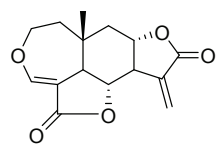
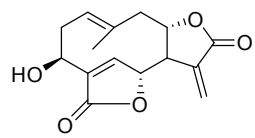
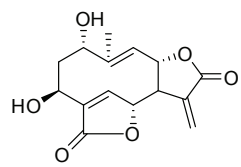
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. cordata	Asia	leaves, stems	deoxymikanolide (**20**), mikanolide (**19**), dihydromikanolide, 11β-hydroxy-13-chloromikanolide acetate, 11β-hydroxy-13-chloromikanolide, 3β-hydroxydeoxymikanolide	 **20**	Kiang et al., 1968; Aguinaldo et al., 1995
M. micrantha	Central and South America and widespread in all regions of Asia-Pacific	aerial parts	mikamicranolide (**21**), dihydromikanolide, deoxymikanolide, mikanokryptin	 **21**	Herz et al., 1975; Huang et al., 2004
M. cordifolia	America and throughout Brazilian territory	aerial parts	mikamicranolide, 11β,13-dihydromikamicranolide (**22**), 3α-hydroxy-11β,13-dihydrodeoxymikanolide, 2β,3β-dihydroxy-11β,13-dihydrodeoxymikanolide	 **22**	Huang et al., 2004; Oliveira et al., 2007
M. urticifolia	Province of Chaco and Córdoba in Argentina and western region of Entre Rios and southern Bolivia	aerial parts	miscandenin (**23**), mikanolide (**19**), deoxymikanolid, anhydroscandenolide	 **23**	Gutierrez et al., 1988
M. periplocifolia	Province of Córdoba, Argentina	aerial parts	mikanolide (**19**), 3β-hydroxyisabelin (**24**), deoxymikanolide, scandenolide, 3-acetoxy-11βH,13-dihydroisabelin; miscandenin, 1,2-epoxymiscadenin; mikacynanchifolide, dihydromikanolide, 3β-hydroxy-11βH,13-dihydroisabelin, mikaperiplocolide (**25**)	 **24**  **25**	Gutierrez et al., 1985

Chart 2. Sesquiterpenes lactones in *Mikania* genus. (cont)

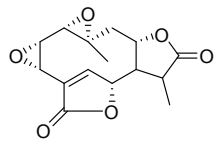
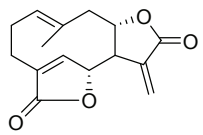
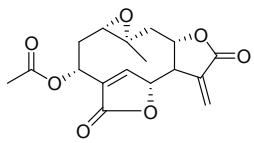
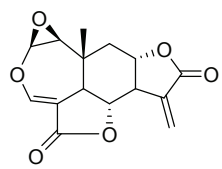
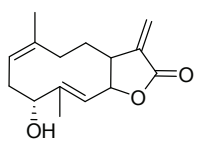
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. mongenansis	Southeast of Cumana, in Caripe, Venezuela	-	dihydromikanolide (**26**), mikanolide (**19**)	 **26**	Mathur and Fermin, 1973
M. dusenii	Northeastern of Argentina and southern Brazil	aerial parts	isabelin (**27**), hydroxyisabelin, mikanolide (**19**), 11βH,13-dihydro-mikanolide, deoxymikanolide, desacetyl-scandenolide	 **27**	Zamorano et al., 1994
M. ypacarayensis	Northeastern of Argentina, southern Brazil and Paraguay	aerial parts	mikanolide (**19**), scandenolide (**28**), 11βH,13-dihydromikanolide, deoxymikanolide, dihydroscandenolide, anhydroscandenolide, 3β-hydroxyisabelin (**24**), 3β-acetoxyisabelin, miscandenin, 3β-methoxyisabelin, 3-dehydroxymikaperiplocolide, 3-acetoxymikaperiplocolide	 **28**	Zamorano et al., 1995
M. cynanchifolia	Brazil	aerial parts	miscandenin (**23**), 1β,2β-epoxymiscandenin (**29**), 3β-hydroxyisabelin, 3β-acetoxy-11β,13-dihydroisabelin	 **29**	Bohlmann et al., 1984
M. minima	Province of Tucumán, Argentina	aerial parts	(6*S*,7*R*,8*S*)-8,15-diacetoxy-14-hydroxymelampa-1(10),4,11(13)-trien-12,6-olide, (6*S*,7*R*,8*S*)-8,15-diacetoxy-14-oxomelampa-1(10),4,11-(13)-trien-12,6-olide, 14-acetoxyartemisiifolin-6α-*O*-acetate, germacranolides, heliangolide (**30**), melampolides, elemadienolides	 **30**	Barrero et al., 2000; Cuenca & Catalán, 1990; Cuenca et al., 1993

Chart 2. Sesquiterpenes lactones in *Mikania* genus. (cont)

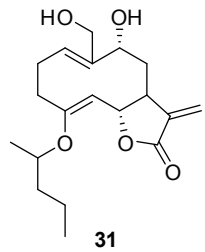
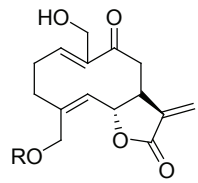
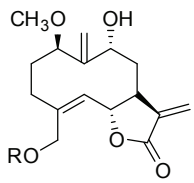
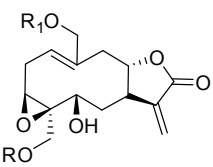
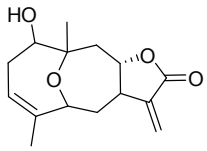
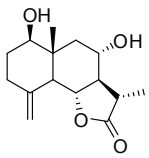
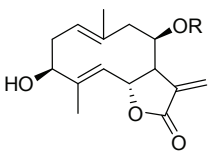
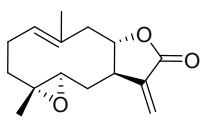
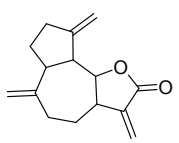
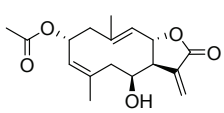
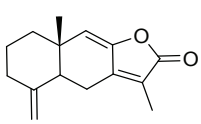
Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. guaco and M. holwayana	Central America	aerial parts	9α,14-dihydroxy-15-isobutyryloxy-costunolide (**31**), 2α-acetoxy-14-hydroxy-15-isovaleryloxy-9-oxo-costunolide, 2α-acetoxy-14-hydroxy-15-(2-methylbutyryloxy)-9-oxo-costunolide, 14-hydroxy-15-isobutyryloxy-9-oxo-costunolide; 15-isovaleryl-miguanin, 15-(2-methyl-butyryl)-miguanin, 1α-methoxy-15-isobutyryloxy-9-oxo-germacra-4-*trans,*10(14),11(13)-trien-12,6α-olide, 14-hydroxy-15-isovaleryloxy-9-oxo-melampolide (**32**), 14-hydroxy-15-(2-methylbutyryloxy)-9-oxo-melampolide, 1β-methoxy-15-isovaleryloxy-9-oxo-germacra-4-*trans*,10(14),11(13)-trien-12,6α-olide, 1β-methoxy-15-(2-methylbutyryloxy)-9-oxo-germacra-4-trans,10(14),11(13)-trien-12,6α-olide, 1α-methoxy-15-isovaleryloxy-9-oxo-germacra-4-*trans*,10(14),11(13)-trien-12,6α-olide, 1β-methoxy-15-isobutyryloxy-9-oxo-germacra-4-trans,10(14),11(13)-trien-12,6α-olide (**33**), 1α-methoxy-15-(2-methylbutyryloxy)-9-oxo-germacra-4-trans,10(14),11(13)-trien-12,6α-olide	 **31**  **32** R=*i*-val  **33** R=*i*-but	Rüngeler et al., 2001; Castro et al., 1989
M. thapsoides	Corrientes Province, Argentina	aerial parts	1(10)E-(3*S*,4*R*,5*R*,7*S*,8*S*)-14-acetyloxy-3,4-epoxy-5-hydroxy-15-senecioyloxygermacra-1(10),11(13)-dien-8,12-olide (**34**), 1(10)E-(4*R*,5*R*,7*S*,8*S*)-4,5-epoxy-14-oxo-15-senecioyloxygermacra-1(10),11(13)-dien-8,12-olide, 1(10)E-3*Z*-(5*R*,7*S*,8*S*)-14-acetyloxy-5-hydroxy-15-senecioyloxygermacra-1(10),3,11(13)-trien-8,12-olide, 1(10)E-(3*S*,4*R*,5*R*,7*S*,8*S*)-14-acetyloxy-3,4-epoxy-5-hydroxy-15-isovaleroyloxygermacra-1(10),11(13)-dien-8,12-olide (**35**), 1(10)E-3*Z*-(5*R*,7*S*,8*S*)-14-acetyloxy-5-hydroxy-15-isovaleroyloxygermacra-1(10),3,11(13)-trien-8,12-olide, 1(10)E-4*Z*-(7*S*,8*S*)-14-oxo-15-senecioyloxygermacra-1(10),4,11(13)-trien-8,12-olide, 1(10)E-4*Z*-(7*S*,8*S*)-14-oxo-15-isovaleroyloxygermacra-1(10),4,11(13)-trien-8,12-olide, 1(10)E-(3*S*,4*R*,5*R*,7*S*,8*S*)-3,4-epoxy-5,14-dihydroxy-15-senecioyloxygermacra-1(10),11(13)-dien-8,12-olide (**36**)	 **34** R_1=Ac; R_2=Sen **35** R_1=Ac; R_2=*i*-val **36** R_1=H; R_2=Sen	Catalán et al., 2003

Chart 2. Sesquiterpenes lactones in *Mikania* genus. (cont)

Plant specie	Geographic distribution	Part used	Compounds	Structure	Reference
M. purpurascens	Northeastern Brazil	roots and aerial parts	purpurascenolide (**37**)	 **37**	Bohlmann et al., 1982b
M. pohlii	Northeastern Brazil	roots and aerial parts	eudesmanolide (**38**)	 **38**	Bohlmann et al., 1982a
M. haenkeana	Jungles of Ecuador, Peru, Bolivia and northwestern of Argentina	aerial parts	germacradienolides (**39**), provincialin, heliangolides, guaianolide, cadinanolide	 **39**	Cuenca et al., 1992
M. mendocina	Provinces of Mendoza and Neuquén, in Argentina	aerial parts	quadragolide (**40**), guaianolide, germacranolide	 **40**	Bardón et al., 1996
M. hoehnei	Brazil between Rio de Janeiro and Santa Catarina state	dried and powdered whole plants	dehydrocostuslactone (**41**), 8β-hydroxyzaluzanin	 **41**	Chaves & Oliveira, 2003
M. grazielae	Northeastern Brazil	aerial parts	2α-acetoxyeupatolide (**42**), 2α-acetoxylaurenobiolide	 **42**	Bohlmann et al., 1982b
M. banisteriae	State of Pará, Brazil	aerial parts	*ent*-kaur-16-en-18-oic acid, *ent*-kaur-16-en-18-ol, 18,19-diacetoxy-*ent*-kaur-16-ene, 17-oxo-*ent*-kaur-15(16)-en-18-oic acid, eudesma-4(15),7(11)-dien-8β,12-olide, eudesma-4(15),7(11),8(9)-trien-12-olide (**43**)	 **43**	Lobitz et al., 1997

Diterpenes

Some diterpenes are common in *Mikania* genus like kaurenoic acid (**44**), the main component of ethanolic extract in *M. obtusata* (Alves et al., 1995) and *M. glomerata* (Barbosa et al., 1994), which is characterized by its trypanocidal activity. Also, the kaurenoic acid has other important activities such as antimicrobial, antinociceptive, anti-inflammatory and smooth muscle relaxant (Costa-Lotufo et al., 2002; Wilkens et al., 2002; Cunha et al., 2003; Gasparetto et al., 2012).

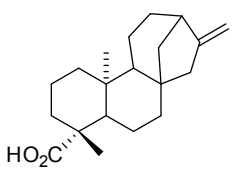
In *M. laevigata* the main representatives are cinnamoylgrandifloric acid (**45**), isopropiloxi-grandifloric acid, isobutiloxi-grandifloric acid and kaurenol (Oliveira et al., 1984; Bighetti et al., 2005; Yatsuda et al., 2005; Santos et al., 2006; Bolina et al., 2009). Furthermore, from *M. oblongifolia* aerial parts were obtained cinnamoylgrandifloric and others terpenes (Vichnewski et al., 1977).

Cruz & Roque (1992) isolated from *M. triangularis* stems, found in the state of São Paulo, Brazil, a new diterpene acid, methyl *ent*-7-α-hidroxypimara-8,15-dien-19-oate and other diterpene acids known as methyl-*ent*-pimara-9(11),15-dien-19-oate (**46**), methyl-*ent*-pimara-8,15-dien-19-oate (**47**), methyl-8,9α-epoxy-*ent*-pimara-15-en-19-oate (**48**), methyl-7β-hydroxy-*ent*-pimara-8,15-dien-19-oate and methyl-7α-hydroxy-*ent*-pimara-8,15-dien-19-oate. In addition, the acidic fraction of hexane extract is composed of various pimaradienes acids, which show antibacterial activity (Cruz et al., 1996).

In a study performed by Nunez et al. (2004) on leaves of *Mikania* sp. nov., found in the state of Bahia, Brazil, several diterpenes were obtained: labda-8(17),12,14-trien-19-oic methyl ester (**49**), pimara-9(11),15-dien-19-oic methyl ester, labda-8(17),13(16),14-trien-19-oic methyl ester, labda-12α-epoxy-8(17),14-dien-19-oic methyl ester, labda-12β-epoxy-8(17),14-dien-19-oic methyl ester (**50**), erythroxyla-3,15-dien-19-oic acid (**51**), labda-12,15-epoxy-8(17),13-dien-19-oic acid (**52**), and labda-12,13-dihydroxy-8(17),14-dien-19-oic methyl ester.

Phytosterols/terpenoids

The most common phytosterols present in approximately 10% of species of *Mikania*, that has its chemical composition determined, are stigmasterol (**53**), lupeol (**54**) and sitosterol. These compounds have been detected in the aerial parts and are found in the species *M.micrantha* (Herz et al., 1975; Nicollier & Thompson, 1981), *M. glomerata* (Barbosa et al., 1994), *M. cordata* (Kiang et al., 1968; Aguinaldo et al., 1995), *M. cordifolia* (Oliveira et al., 2006), *M. minima* (Cuenca & Catalán, 1990), *M. hoehnei* (Chaves & Oliveira, 2003), *M. grazielae* (Bohlmann et al., 1982b), *M. pseudohoffmanniana* (Souza et al., 2006), *M.*



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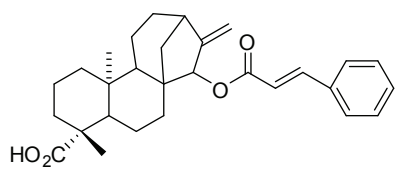

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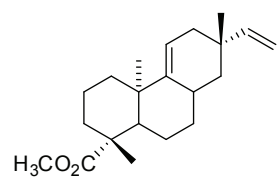

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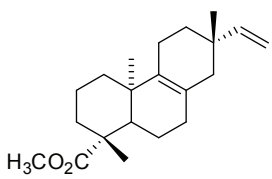

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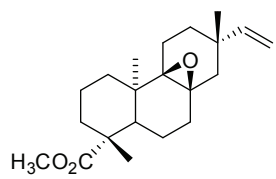

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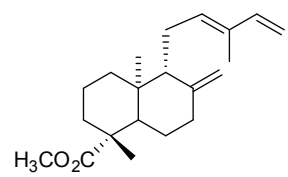

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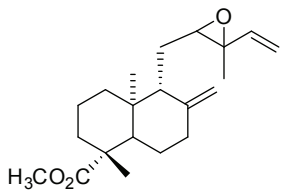

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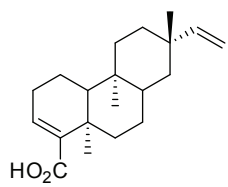

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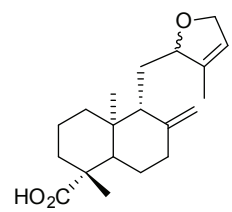

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stipulacea (Nascimento & Oliveira, 2001; Nascimento et al., 2004) and *M. pohlii* (Bohlmann et al., 1982a).

The presence of other common phytosterols as campesterol and taraxasterol has been reported in species like *M. cordifolia* (Oliveira et al., 2006), *M. laevigata* (Ferreira & Oliveira, 2010), *M. hoehnei* (Chaves & Oliveira, 2003) and *M. parodii* (Gregorio et al., 2008).

The terpenoids amyrin and friedelin (**54**), abundant in *Mikania* genus, were reported in *M. micrantha*, *M. cordata*, *M. cordifolia* (Oliveira et al., 2006), *M. minima* and *M. lasiandrae* (Soares et al., 2007), among others species. Other terpenoids less common but equally important for their antioxidant activity, such as squalene, were found in several species like *M. grazielae* (Bohlmann et al., 1982b), *M. sessilifolia* (Bohlmann et al.,1981), *M. luetzelburgii* (Bohlmann et al., 1981) and *M. officinalis* (Bohlmann et al., 1981).

Among the exotic representatives of terpenoids present in *Mikania* genus were reported τ-muurolol in *M. hookeriana* (Reis et al., 2003), stigmasta-4,22-dien-3-one in *M. microptera*, olean-9(11),13-dien-3-one in *M. rimachii* (Díaz et al., 1992) and 19,20-dihydroxy-16-oxo-geranyl from *M. luetzelburgii* (Bohlmann et al., 1981).

Flavonoids

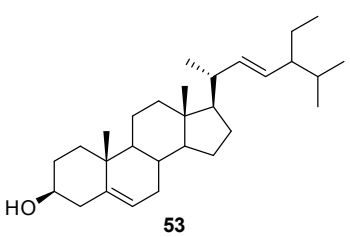
Flavonoids are popular due to their antioxidant activity and are widely present in *Mikania* genus supporting its pharmacological activity. In *M. laevigata* flavonoids glycosides as patuletin 3-*O*-β-D-glucopyranoside (**56**), kaempferol 3-*O*-β-D-glucopyranoside (**57**), quercetin 3-*O*-β-D-glucopyranoside (**58**) and 3,3',5-trihydroxy-4',6,7-trimethoxyflavone are the representatives compounds (Ferreira & Oliveira, 2010). In *M. cordata*, flavonoids were described as patuletine-3-*O*-β-D-6"-(p-coumaroyl), glucoside (6-methoxyquercetin-3-*O*-β-D-6"-(*p*-coumaroyl)glucoside), mikanin-3-*O*-sulfate (salt as Ca^{+2}) (**59**), eupalitin-3-*O*-sulphate (as salt K^{+}) (**60**), eupalitin-3-*O*-β-D-glucoside (**61**), 6-methoxykaempherol-3-*O*-β-D-glucoside (**62**), nepetin (**63**) and kaempherol-3-*O*-α-L-rhamnoside (**64**) (Aguinaldo et al., 2003). For the same species, it was reported the isolation of a flavone, mikanin-(3,5-dihydroxy-4',6,7-trimethoxyflavone) with epifriedelinol from roots and fumaric acid from leaves and stems (Kiang et al., 1965).

In *M. cordifolia* a quercetin derivative was identified as quercetin-3-*O*-glucoside. In *M. micrantha* was isolated and identified eupalitin, eupafolin, luteolin (**65**) (Wei et al., 2004), mikanin, alpinetin, mikanin-3-*O*-sulfate (**59**) (Herz et al., 1975; Nicollier & Thompson, 1981; Boeker et al., 1987; Cuenca et al., 1988; Jiang et al., 2001). In the same specie was identified 3,4',5,7-tetrahydroxy-6-methoxyflavone-3-*O*-β-D-glucopyranoside by Huang et al. (2009). Kaempferol-3-*O*-glucoside (**57**) and quercetin-3-*O*-glucoside (**58**) were identified from *M. parodii* (Gregorio et al., 2008). Naringenin (**66**) was identified from *M. grazielae* (Bohlmann et al., 1982b) and a specific flavone derivative called batatifolin was found in *M. batatifolia* (Herz & Santhanam, 1969).

Caffeoylquinic acid and derivatives

The chemical compound 5-caffeoylquinic acid is a caffeic acid ester, also known as a chlorogenic acid, commonly found in a wide number of plants, *e.g.* coffee. It is produced in plants via an ester bond between the carboxyl group of caffeic acid and the 5-hydroxyl group of quinic acid (Clifford et al., 2006). The chlorogenic acid and caffeic acid were reported as dampening the risk of chronic diseases such as inflammation, cardiovascular diseases and cancer (Boyer & Liu, 2004; Bonita et al., 2007).

In *M. micrantha* was reported the presence of 3,5-di-*O*-caffeoylquinic acid n-butyl ester and 3,4-di-*O*-caffeoylquinic acid *n*-butyl ester (Wei et al., 2004). The same 3,5-di-*O*-caffeoylquinic acid (**67**) was reported in *M. cordifolia*, beyond others derivatives like 5-*O*-caffeoylquinic acid, 3,4-di-*O*-caffeoylquinic acid (**68**), 4,5-di-*O*-caffeoylquinic acid and 3-*O*-feruloyl,5-*O*-caffeoylquinic acid (Gregorio et al., 2008). In *M. lasiandrae* was also reported the presence of caffeoylquinic acid (Soares et al.,2007). In *M. hirsutissima* was reported the presence of 1,5-dicaffeoyl-quinic acid (Oliveira, 1972; Ohkoshi et al.,2004).



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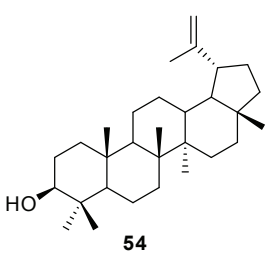

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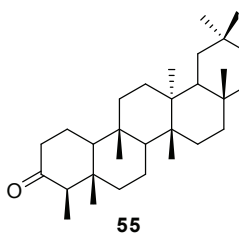

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Pharmacological activities

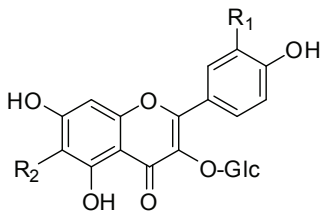
A given plant provides the investigator with a complex library of unique bioactive constituents and can be an advantageous strategy to prospect new pharmacological compounds. The task of the natural products researcher is to select those compounds of pharmacological interest through bioassay-guided fractionation of the "natural combinatorial libraries" produced by extraction, and then to collaborate in the optimization and development of the lead natural product structure.

The *Mikania* species have multiple pharmacological actions. In general, activity in respiratory tract, anti-inflammatory, anti-allergic, analgesic, antioxidant even in system nervous central. In this section, our aim is to highlight the pharmacological experiments and studies reported with species of the genus *Mikania*.

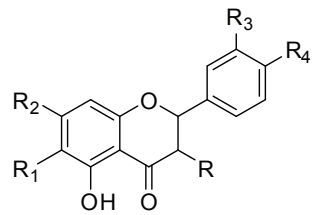
Activity in the respiratory tract

Medicinal plants play an important role in maintaining public health, mainly due to their low cost and availability. Some plants acting in the respiratory system, such as *Mikania* genus, have confirmed their effectiveness. For example, *M. glomerata*, one of the most important and commonly used species *Mikania* genus, has been popularly used in the treatment of asthma, bronchitis and coughing (Teske & Trentini, 1997; Silva et al., 2006; Agra et al., 2008). Other species, known as "guaco" are also used to treat respiratory problems as *M. cordifolia* (Oliveira et al., 2006, Caribe & Campos, 1991), *M. laevigata* (Bolina et al., 2009) and *M. cordata* (Ali et al., 2011)

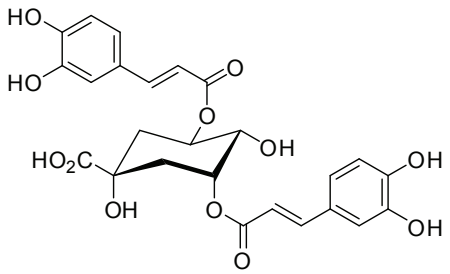
Other studies have shown the use of *M. glomerata* and *M. laevigata* as expectorant, in the treatment of influenza and respiratory diseases (Lorenzi & Matos, 2002; Gasparetto et al., 2010). The coumarin seemed to be partially responsible for the bronchodilator activity of the plant through the relaxation of smooth muscle. In addition, Moura et al. (2002) verified that the aqueous and hydro-alcoholic extracts (HAE) obtained from *M. glomerata* induced a significant inhibition on the histamine contractions on the isolated guinea-pig trachea. HAE induced a concentration-dependent relaxation on guinea-pig trachea precontracted with histamine (IC50 0.34 mg mL^{-1}), acetylcholine (IC50 0.72 mg mL^{-1}) or K^+ (IC50 1.41 mg mL^{-1}) and on isolated human bronchi precontracted with K^+ (IC50 0.34 (0.26-0.42) mg mL^{-1}). In studies evaluating the HAE of *M. laevigata* for the treatment of respiratory diseases it was found that the extract produced a dose dependent relaxation in denuded and intact rat epithelium tracheal



56 R_1=R_2=OH
57 R_1=R_2=H
58 R_1=OH; R_2=H



59 R=$(OSO_3)^-Ca^{+2}$; R_1=R_2=R_4=OCH_3; R_3=H
60 R=$(OSO_3)^-K^+$; R_1=R_2=OCH_3; R_3=H; R_4=OH
61 R=*O*-β-D-Glc; R_1=R_2=OCH_3; R_3=H; R_4=OH
62 R=*O*-β-D-Glc; R_1=R_3=H; R_2=R_4=OH
63 R=H; R_1=OCH_3; R_2=R_3=R_4=OH
64 R=*O*-α-L-Rha; R_1=R_3=H; R_3=R_4=OH
65 R=R_1=H; R_2=R_3=R_4=OH
66 R=R_1=R_3=H; R_2=R_4=OH



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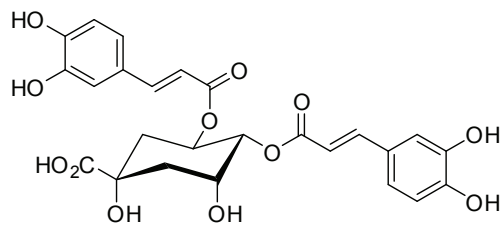

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precontracted with acetylcholine with an effective concentration (EC50) of 1406.7 µg/ml and 1378.3 µg/ml respectively, and a maximum effect (E_{max}) of 94.7 and 95.7% respectively (Graça et al., 2007; reviewed in Gasparetto et al., 2012). These data supports the indication that *M. glomerata* and *M. laevigata* can be used to treat bronchoconstrictive respiratory diseases.

Activity in the digestive system

Many plants and their extracts are commonly used for acting against several disorders of the digestive system. Among them are some species of the genus *Mikania* as *M. glomerata*, *M. laevigata* and *M. cordata*.

In a study performed by Salgado et al. (2005) with *M. glomerata*, the aqueous extract of leaves (1000 mg/mL) showed a decrease in the propulsive movements of the intestinal contents in mice. Oral administration produced an inhibition of gastrointestinal transit as effective as that produced by loperamide, a reference antidiarrheal drug. These findings suggested that the aqueous extract of the leaves of *M. glomerata* might elicit an antidiarrheal effect by inhibiting intestinal motility.

Moreover, the decoction of the leaves of *M. cordata* also shows effects in the digestive system. It is used in dyspepsia, dysentery and gastric ulcer (Ghani, 1998). The methanolic fraction of root extract showed antiulcer effects in male Sprague-Dawley rats in a dose dependently manner inhibiting gastric ulcers induced by water immersion stress-induced, ethanol, aspirin and phenylbutazone. The ED50 values of the extract in the above four ulcer models were found to be 95.1, 109.7, 125.5 and 136.2 mg/kg, respectively (Bishayee & Chatterjee, 1994b). In the study realized by Paul et al. (2000) the alkaloid fraction obtained from an ethanolic extract of leaves of *Mikania cordata* (dose 50 mg/kg) exhibited antiulcer activity (*in vivo*) in gastric erosions induced by diclofenac sodium in rats Long Evans. Mosaddik & Alam (2000) carried out a similar study to evaluate the role of alkaloids fraction in gastric erosions induced by diclofenac sodium in rats Long Evans and found that in the alkaloidal-administered group (50 mg/kg) the ulcer index of the stomach (0.268±0.0346) and of the duodenum (0.050±0.0129) were significantly lower than the diclofenac-only administered group (0,691±0,0184 and 0.093±0.0346, respectively). Thus, bioactive principles of *M. cordata* have proved anti-ulcerogenic effects.

The crude hydroalcoholic 70% extract of *M. laevigata* presents antiulcerogenic activity when applied in male Wistar rats decreasing the ulcerative index produced by indomethacin, ethanol, stress and reserpine by 85, 93, 82 and 50%, respectively (Bighetti et al., 2005). In this way, different species of "guaco" show activity in the digestive system.

Effect on nervous system

Mikania extracts possesses some neuropharmacological properties confirmed. The studies with methanolic fraction of *M. cordata* root extract on experimental animals caused alterations in the general behavior pattern (*e.g.* reduction in spontaneous motility, analgesia, and suppression of aggressive behaviour), suppression of conditioned avoidance response and showed antagonism to amphetamine toxicity. The observations suggest that the root of *M. cordata* possesses a potent central nervous system-depressant action (Bhattacharya, et al. 1988).

The hydroacoholic extract of aerial parts from *M. scandens* presents neuropharmacological properties in Swiss albino mice. The results of the present study revealed significant and dose-dependent (250 and 500 g/kg body weight) central antinociceptive, locomotor depressant, muscle relaxant, and sedative potentiating effects of the extract, demonstrating its depressant action on the central nervous system (Dey et al., 2011).

Anti-inflammatory, anti-allergic and analgesic activity

The inflammatory response is associated with a range of diseases and it is difficult to establish an effective therapy to control the inflammatory processes. So, there is a clear and obvious need to search for new medicinal compounds, especially those derived from plants. Studies with extracts, oils and compounds of several species have demonstrated their important activity. Oliveira et al. (1985) discovered the anti-inflammatory action of the fluid extract of *M. glomerata* through the antiedema activity test in the rat paw induced by carrageenan and quantified by plethysmography. These inhibitions were slightly smaller than that produced by the control with phenylbutazone.

In addition, Leite et al. (1993) compared the effects of hydroalcoholic extract of *M. glomerata* and solution of coumarin (1,2-benzopyran), undergoing tests *in vivo* (paw edema). The results showed anti-inflammatory effect for the extract and also the solution. The different intensity on pharmacological effects indicates that coumarin has contributed to the pharmacological effect with other chemicals in the extract in a synergic action. Ruppelt et al. (1991) studied the "guaco" tea (*M. glomerata*) as analgesic and anti-inflammatory evaluating the number of contortions in mice and diffusion of Evans blue dye in the peritoneum. The mice group that ingested the tea showed inhibition of 63.1% in contortions and a reduction of 48.92% in

diffusion of the dye in comparison with the control group. In this way the plant infusion demonstrated analgesic and anti-inflammatory activity in lesser degree in comparison with the analgesic control.

The compound scandenolide, a sesquiterpene lactone present in *M. cordata*, exhibited anti-inflammatory activity. It also inhibited the production of leukotriene B4 and 5-HETE with IC50 of 15 and 30 µM concentration, respectively (Ysrael & Croft, 1990). The anti-inflammatory activity of *M. cordifolia* was attributed to the presence of dicaffeoylquinic acids and was evaluated trough activity on monocyte migration and superoxide anion production (Peluso et al., 1995).

Other species, *M. laevigata* and *M. involucrata* demonstrated a potential anti-inflammatory activity in inhibiting oedema and pleurisy. In the induced rat paw oedema test, the animals treated with leaf decoctions of *M. laevigata* (200 mg/kg) and *M. involucrata* (50 mg/kg) presented an edema inhibition of 81.56 and 81.67%, respectively, 3 h after the administration of the phlogistic agent. In the pleurisy assay, *M. laevigata* (400 mg/kg) and *M. involucrata* (200 mg/kg) leaf decoctions inhibited leukocyte migration to the pleural exudate by 28.26 and 54.35%, respectively (Suyenaga et al., 2002).

The hydroalcoholic extract of *M. glomerata* and *M. laevigata* also affected the inflammatory and oxidative stress caused by a single coal dust intratracheal instillation in rat. Histopathological analyses revealed that animals pretreated subcutaneously with the hydroalcoholic extract (100 mg/kg) had a reduction in lung inflammation, with an additional decrease in protein thiol levels, suggesting that guaco has an important protective effect on the oxidation of thiol groups (Freitas et al., 2008).

The analgesic activity of hydromethanol extract of leaves from *M. scandens* was determined for its central and peripheral pharmacological actions using hotplate and tail immersion method and acetic acid-induced writhing test in mice respectively. The extract (250 and 500 mg/kg), produced a significant increase in pain threshold in hotplate and tail immersion methods in a dose dependent manner. In acetic acid-induced writhing test, the extract (500 mg/kg) produced a maximum of 53.73% inhibition of writhing reaction compared to the reference drug Diclofenac-Na (76%). Thus, the results suggested that the extract has a strong analgesic effect (Hasan et al., 2009). In addition, the crude extract of *M. cordata* (1 and 3 g/kg) and a sesquiterpene lactone deoxymikanolide (10 mg/kg) significantly inhibited acetic-acid induced writhing in mice (Ahmaed et al., 2001).

Another important activity observed in some species is the anti-allergic activity. Fierro et al. (1999) observed this activity in their study with *M. glomerata*. A fraction (MG1) obtained from the ethanolic extract used as an anti-allergic and anti-inflammatory agent was evaluated for these properties on ovalbumin-induced allergic pleurisy and in models of local inflammation induced by biogenic amines, carrageenan and PAF. Plasma exudation as well as neutrophil and eosinophil infiltration evoked by the intrapleural injection of the antigen were significantly reduced by the fraction. Likewise, PAF-induced pleural neutrophil migration was inhibited by the treatment with MG1. The results suggest that MG1 is effective in inhibiting immunologic inflammation. In conclusion, many species of *Mikania* are involved in anti-inflamatory, analgesic and anti-allergic responses.

Antimicrobial, antivirucidal and antiparasitic activity

The antimicrobial and antiparasitic properties of compounds present in plants as products of secondary metabolism have been known empirically for centuries, but only recently they have been scientifically confirmed. Extracts and essential oils from plants proved their efficacy in controlling the growth of a wide variety of microorganisms, including bacteria, fungi, parasites and others.

Staphylococcus aureus PI57 is a bacterium that resists to all antibiotics used in medical practice with the exception of vancomycin. In a study carried out with hexanic extract of *M. glomerata*, it was observed the inhibition growth of a multiresistant strain of *Staphylococcus aureus* PI57, verified by antibiogram and bioautography (Amaral et al., 2003). Other studies have shown antibacterial activity of *M. glomerata* extract, supporting its action against *S. aureus* (Pessini et al., 2003; Duarte et al., 2004).

In a study performed by Yatsuda et al. (2005), the hexane fraction of extracts from *M. laevigata* was the most effective in inhibiting the growth of mutans streptococci (MIC values between 12.5 µg/mL and 400 µg/mL, and MBC values between 25 µg/mL and 400 µg/mL). In addition, sub-MIC levels of the crude extracts and their hexane fractions inhibited the adherence of the microorganisms to a glass surface.

In addition, the acidic fraction of hexane extract from *M. triangularis*, composed of various pimaradienes acids, showed antibacterial activity (Cruz et al., 1996).

But et al. (2009) carried out a study with *M. micrantha* and the compound 1,10-epoxy-4-germacrene-12,8,15,6-diolide showed activity against respiratory syncytial virus (IC50 37.4 µM) and parainfluenza virus type 3 (IC50 37.4 µM). Additionally potassium mikanin 3-sulfate showed inhibitory activity against parainfluenza virus type 3 (IC50 19.7 µM).

The biological activities described for *M. cordifolia* include antitrichomonal and antitrypanosomal (Arias et al., 1995; Serrano et al., 2000). The diterpene *ent*-kaur-16-en-19-oic acid (kaurenoic acid), the main component in ethanolic extract of *M. obtusata*, has trypanocidal activity determinated by Alves et al. (1995). This compound showed IC50 of 0.5 mg/mL (1.66 mM) against trypomastigote forms of *Trypanosoma cruzi,* the causative agent of Chagas disease. Furthermore, the ethanolic extract reduced significantly the number of parasites in the blood. The compound also showed antibacterial and antifungal activities (Mathur et al., 1975; Oguntimein, 1987). Other species that showed in vitro trypanocidal properties were *M. hoehnei* and *M. stipulaceae*. The diterpene *ent*-9α-hydroxy-15β-*E*-cinnamoyloxy-16-kauren-19-oic acid obtained from *M. stipulacea* diterpene was active towards *T. cruzi* tripomastigotes, reducing their number by 61.7, 62.8 and 69.4% at 100, 250 and 500 µg/mL and the sesquiterpene lactone 8β-hydroxyzaluzanin isolated from *M. hoehnei* killed 56.6 and 81.0% of the parasites at the concentration of 250 and 500 µg/ml (Nascimento et al., 2004).

Antiophidic activity

Although serotherapy was discovered one hundred years ago, many rural communities do not have access to antivenoms. In this way, they alternatively use plants with antiophidic activity known in popular culture, such as some species of the genus *Mikania*.

The antiophidic effect of coumarin present in *M. glomerata* was tested against the venom of *Bothrops jararaca* snake and the animal survival rate was evaluated resulting in 40% survival in animals that received treatment comparing to 0% in the control group (Pereira et al., 1994). In the same way, Maiorano (2005) observed the antiophidic activity of *M. glomerata* root extracts that reduced the hemorrhage zone stimulated by the intradermal injection of *Bothrops* venom by 80% in rats. This result suggests that there is an interaction between the components of guaco and metalloproteases involving the catalytic sites of these enzymes or essential metal ions, thereby inhibiting their hemorrhagic activities (reviewed in Gasparetto et al., 2012). The aqueous extract of *M. cordifolia* is also used by ancient rainforest inhabitants to treat snake bites (Caribe & Campos, 1991).

The activity of *M. guaco* in oral administration was confirmed by Gutierrez (1993). The extract components were effective in mammals to inhibit the letal effects of poisonous animals, such as nauyaque snake and rattlesnake, scorpions, spiders and bees. The author has indicated its use for treating snake bites, scorpion stinging, bee sting and similar.

Antimutagenic and cytotoxic activity

The natural products provide very important chemical libraries that have led to new antimutagenic drugs (Cragg et al. 2009). The antimutagenic activity of *M. laevigata* was reported by Fernandes & Vargas (2003). They observed an inhibition of the mutagenic effect induced by 2-amino fluorene and sodium azide using the plant extract, and a synergistic effect in the presence of 4-nitroquinoline-1-oxide in *Salmonella*/ microsome assay.

Melampolides isolated from *M. minima* were identified as (6S,7R,8S)-8,15-diacetoxy-14-hydroxymelampa-1(10),4,11(13)-trien-12,6-olide and (6S,7R,8S)-8,15-diacetoxy-14-oxomelampa-1(10),4,11-(13)-trien-12,6-olide which present cytotoxic activity. This activity was tested against three tumor cell lines, and IC50 values were observed in the order of 10^{-6} M. The former compound showed an activity level similar to that of salonitenolide diacetate and the later showed a higher activity (Barrero et al., 2000). Differently, the mikanolide, dihydromikanolide and others sesquiterpenes lactones derivatives from *Mikania* genus were indicated as DNA polymerase inhibitors by Teng et al. (2001).

The chemopreventive role of *M. cordata*, was evaluated for its effects on phase 1 and 2 of the hepatic drug detoxifying enzyme system in rats (Bishayee & Chatterjee, 1994a). In oral doses of 50, 100, or 150 mg/kg of extract for 4, 8 or 12 weeks results in dose-dependent effects on a marked induction of uridine diphosphoglucuronyl transferase activities of liver microsomes and others effects. The study indicated that the carcinogens would be reduced by specific enhancement of drug-detoxifying enzymes in the liver of rats treated with the plant extract.

The Chart 3 summarizes other pharmacological applications recently reported in literature.

Other potential uses

Allelopathic activity

Allelopathy is defined as any indirect or direct, beneficial or damaging effect, from a plant to other, resulted from the production of chemical products which are released into the environment. The same chemical compounds responsible for the allelopathic activity can be modulated in some pharmacological activity. It has also attracted great interest due to their potential applications in agriculture and therefore has been studied in several plants. The ethanolic extracts of *M. laevigata* traditionally cultivated in the soil or in a hydroponic system were tested for allelopathic activity. Allelopathic activity was evaluated by the inhibition of

germination assay using lettuce seeds. An allelopathic effect was observed for both extracts, although a more expressive activity of traditional "guaco" was verified, since the inhibition of seeds germination was 100%, even in the lower concentration (Baratto et al., 2008).

Other species of this genus, the *M. micrantha*, also showed allelopathic activity. The aqueous, essential oil and terpenoid fractions exhibit the inhibitory activity against the germination and the growth of several plant species (Nicollier & Thompson, 1981; Ismail & Chong, 2002). Some allelopathic phenolic acids have been detected from the aqueous fraction of *M. micrantha* (Ismail & Chong, 2002). Other study has indicated that chloroform and ethyl acetate extracts have significant reduction in growth of the seedling. Sesquiterpene lactones and flavone compounds isolated from the chloroform and ethyl acetate also show inhibitory activity (Huang et al., 2009).

Chart 3. Species and other pharmacological potential uses.

Species	Potential use	Reference
M. glomerata	Antispasmodic, sudorifics, antisyphilitics, antipyretic, tonic, anticoagulant, rheumatism, neuralgia, arthritis, itchy eczema, appetite stimulant, antioxidant, antitumoral, antifungal, hemolytic effect against erythrocytes of rats and humans	Barbosa et al., 1994; Guisalberti, 1997; Costa-Lotufo et al., 2002; Lorenzi & Matos, 2002; Wilkens et al., 2002; Vieira et al., 2002; Vicentino & Menezes, 2007; Gasparetto et al., 2010.
M. laevigata	Antiulcer, anti-inflammatory, analgesic, antispasmodic, antimicrobial, anti-allergic	Ruppelt et al., 1991; Suyenaga et al., 2002; Bighetti et al., 2005; Santos et al., 2006.
M. cordata	Coughs, gastrointestinal infections, snake bites and scorpion venom, anti-carcinogenic	Quisumbing, 1978; Bishayee & Chatterjee, 1994a.
M. micrantha	Regulation of plant growth, antifungal, antibacterial, treatment of itch and athlete's foot in Jamaica	Rice, 1984; Picman, 1986; Baruah et al., 1994; Facey et al., 1999.
M. mendocina	Feeding deterrent activity against *Atta cephalotes*	Bardón et al., 1996.
M. obtusata	Anti-inflammatory and cytotoxic activities	Hui et al., 1989.
M. hoehnei	Activity against lymphocytic leukemia P388 in vitro, antifungal activity, inhibitory activity on nitric oxide production, nuclear factor KB and in ethanol absorption	Jolad et al., 1974; Asakawa & Takemoto, 1979; Matsuda et al., 2000; Yoshikawa et al., 2000.
M. guaco	Used as anti-inflammatory drug and against snake and scorpion bites	Morton, 1981.
M. amara	Against fever, whooping cough and rheumatism	Silva et al., 1984.
M. hirsutissima	Treatment of rheumatism, gout, diarrhea; the aqueous ethanolic extract exhibited proliferative activity toward human peripheral blood mononuclear cells; the compounds 2β,16α,17-trihydroxy-ent-kauran-19-oic acid and 3β,16α,17-trihydroxy-ent-kauran-19-oic acid showed significant activity (43.8% and 36.7%, at 100mM) on the lymphocyte	Oliveira, 1972; Ohkoshi et al., 2004.

Phytotoxic activity

The phytotoxic activity of sesquiterpene lactones germacrane type from *M. micrantha* was reported in some studies due the presence of deoxymikanolide, dihydromikanolide and micramikanolide (Herz et al., 1975; Huang et al., 2004). According to Huang et al. (2009), these compounds and 3,4',5,7-tetrahydroxy-6-methoxyflavone-3-*O*-β-D-glucopyranoside showed strong phytotoxicity against B. *parachinensis*, being the deoxymikanolide the most active.

Summary and future perspectives

Out of 430 species identified from genus *Mikania*, 55 of them provide over 300 different chemical compounds, among terpenes and derivatives, some alkaloids, saponins, sterols and flavonoids. From its extensive use as herbal medicine, it was identified several of these compounds as being of highly pharmacological interest due to its actions. Besides the activities already identified other actions were not tested yet, once new studies are carried out it may indicate other interesting features of the molecules already extracted from this genus. The high variability in *Mikania* composition among different species and batches may contribute to equally high variability in activity. In the future, widespread interest in *Mikania* genus seems certain to ensure continued research with this herb. Moreover, interdisciplinary research and the development of modern combinatorial techniques make possible the discovery of novel agents from these species.

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***Correspondence**

Sidnei Moura
Instituto de Biotecnologia, Universidade de Caxias do Sul
95070-560 Caxias do Sul-RS, Brazil
sidnei.moura@ucs.br
Tel.:+55 54 3218 2149