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An Overview of *Miconia* genus: Chemical Constituents and Biological Activities

Gracielle Oliveira Sabbag Cunha[1,2], Danielle Coelho da Cruz[1], Antônio Carlos Severo Menezes[1]

ABSTRACT

Miconia genus, belonging to Melastomataceae family, is widely distributed in tropical America and includes some native Brazilian species. This paper reviews the literature on this genus, focusing on its chemical constituents and biological activities, in order to build the base for further studies. Of about 1050 species of *Miconia*, only 21 were studied from a chemical point of view until the present moment. Among these species, 79 different secondary metabolites were isolated, divided into 7 classes: Flavonoids, triterpenes, phenolic acids, steroids, quinones, tannins and lignans. This chemical diversity gives of the genus interesting biological properties, including antimicrobial, antitumor, antioxidant, antidiabetic, trypanocidal, antileishmanial, schistosomicidal, antimalarial, insecticidal, analgesic and anti-inflammatory activities.

Key words: Melastomataceae, *Miconia*, Natural products, Pharmacological properties, Phytochemistry

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INTRODUCTION

Miconia is one of the most representative genus from Melastomataceae family, with more than 1050 species occurring from western Mexico and the Caribbean to Uruguay and northern Argentina.[1] In Brazil, this genus ranks fifth position in diversity and is represented by 276 species, of which 121 are endemic.[2]

Previous phytochemical investigations on this genus have revealed that the main constituents include flavonoids and triterpenes. Extracts obtained from *Miconia* and their isolated compounds have demonstrated the therapeutic potential of this genus. Some pharmacological properties were evaluated by *in vitro* and *in vivo* preclinical studies, as antimicrobial,[3-10] analgesic,[11-14] anti-inflammatory,[14] antioxidant,[15-17] antitumor[18-22] trypanocidal,[23-24] antileishmanial,[25] schistosomicidal,[26] antimalarial,[27] insecticidal[28,29] and antidiabetic activities.[30]

However, there is no review on its chemical constituents, traditional uses and pharmacological activities. Consequently, this paper was aimed to summarize the current advances in these aspects. A literature search was conducted using the keywords "*Miconia*", "isolated compounds" and "biological activities" on five electronic databases (Web of Science, PubMed, Scopus, Science Direct and ACS Publications) in addition to free search in Google Scholar, to published works until December 2018, without limitation about the language or publication type. Reference lists of the identified works were also searched and additional research traced online. Inclusion criteria were papers reporting the isolation or identification of compounds and biological activities related to the *Miconia* genus.

The review is organized into three main sections. The first section deals with the traditional use of *Miconia* species. In the second section the phytochemical studies of the genus are presented and, finally, the third section presents the studies related to the pharmacological properties of *Miconia*.

Traditional use

Ethnobotanical studies reported varied popular uses of the species of *Miconia* genus. *M. albicans* and *M. mirabilis*, species popularly known as canela-de-velho and capa-de-Xangô, respectively, have been used because of their antirheumatic properties.[31] Hasrat *et al.* (1997)[32] reported the use of *M. ciliate* in traditional medicine from Suriname as diuretic, depurative, sedative and in treatment of sunstroke, itching, sudorific and night sweats. The medicinal use of *M. cinnamomifolia* in the treatment of fever and cold was reported by Boscolo and Valle (2008).[33] In 2001, a survey was carried out next rural communities in the south of Minas Gerais State (Brazil) in order to know which and for what purpose the native species are used in the popular medicine. *M. rubiginosa*, known locally as capiroroquinha, was cited for its use in the treatment of throat affections.[34]

Phytochemistry

Among approximately 1050 species of *Miconia* genus, this review pointed out that only 21 were studied to the moment from the point of view of its chemical composition: *M. stenostachya, M. albicans, M. pepericarpa, M. sellowiana, M. fallax, M. rubiginosa, M. ligustroides, M. ferruginata, M. langsdorffii, M. mac-*

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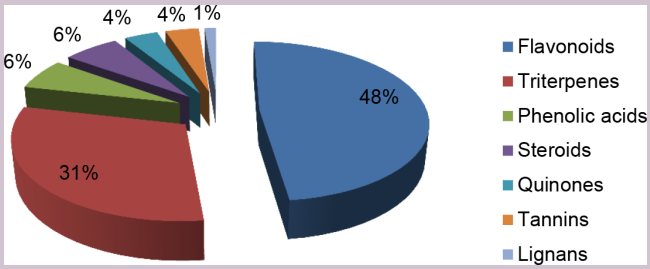


Figure 1: Distribution of 79 isolated compounds of *Miconia* by classes.

rothyrsa, M. affinis, M. lepidota, M. pilgeriana, M. myriantha, M. alypifolia, M. cannabina, M. cabucu, M. willdenowii, M. prasina, M. ioneura and *M. trailii.* 79 different compounds belonging to the class of flavonoids, triterpenes, steroids, phenolic acids, quinones, tannins and lignans have been isolated. The proportion of different compounds of *Miconia* genus is shown in Figure 1.

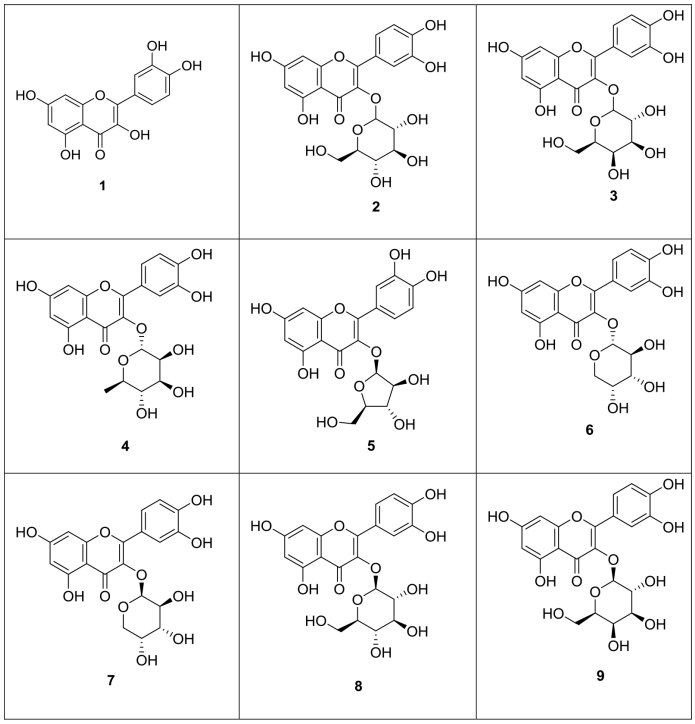
In this section, we described the main chemical components of *Miconia*. The corresponding isolation parts of these compounds and species where they were found are presents in Box 1.

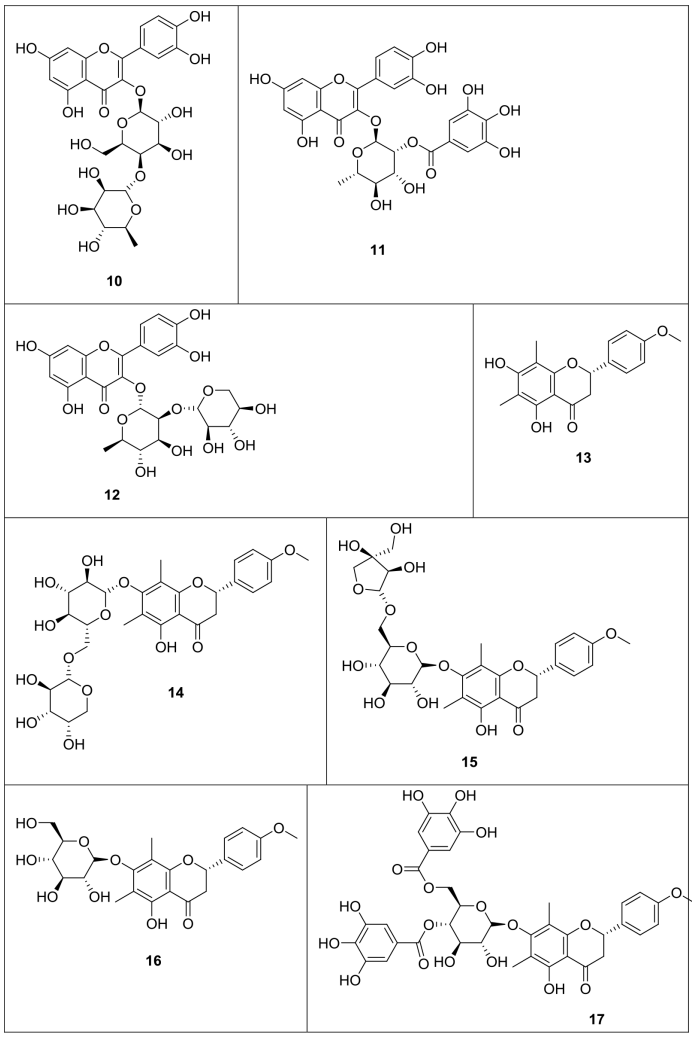
Flavonoids

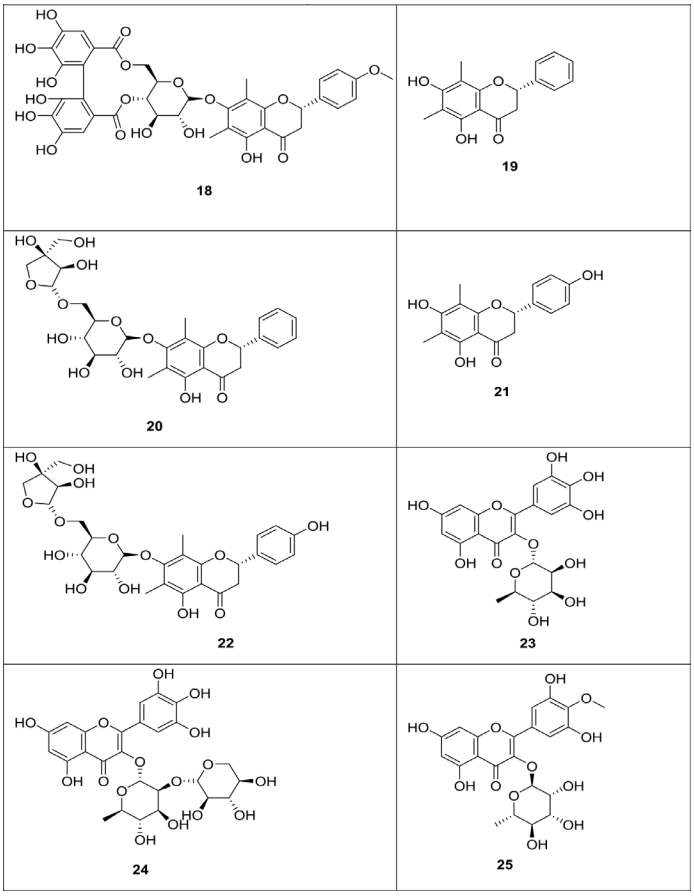
Amid 38 isolated and identified flavonoids from *Miconia*, 28 are glycosylated flavonoids that have sugar units in the carbons 3 or 7 and 10 are aglycones. The aglycone unit most present in these compounds is quercetin, followed by matteucinol and kaempferol. These constituents were identified as quercetin (1), quercetin-3-*O*-glucoside (2),[17] quercetin-3-*O*-galactoside (3),[15] quercetin-3-*O*-α-rhamnopyranoside (4),[9,35,36] quercetin-3-*O*-β-arabinofuranoside (5), quercetin-3-*O*-α-arabinopyranoside (6), quercetin-3-*O*-β- arabinopyranoside (7),[9,35] quercetin-3-*O*-β-glucopyranoside(8),[9,36]quercetin-3-*O*-β-galactopyranoside (9),quercetin-3-*O*-α-rhamnopyranosyl-(1→4)-*O*-β-galactopyranoside(10),[9,35] quercetin-3-*O*-(2″-galloyl)-α-*L*-rhamnopyranoside (11),[30] quercetin-3-*O*-β-xylopiranosyl-(1→2)-*O*-α-rhamnopyranoside (12),[9,36] matteucinol (13),[7,37,38] matteucinol 7-*O*-α-L-arabinopyranosyl(1→6)-β-*D*-glucopyranoside (miconioside A) (14), matteucinol 7-*O*-β-D-apiofuranosyl(1→6)-β-D-glucopyranoside (15),[38] mattucinol-7-*O*-β-D-glucopyranoside (16), mattucinol-7-*O*-[4”,6”-di-*O*-galloyl]-β-D-glucopyranoside (17) mattucinol-7-*O*-[4”,6”-*O*-(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranoside (18),[5] demethoxymatteucinol (19), 7-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyldemethoxymatteucinol (miconioside C) (20), farrerol (21),[37] farrerol 7-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (miconioside B) (22),[37,38] myricetin-3-*O*-α-rhamnopyranoside (23),[9,30,36] myricetin-3-*O*-β-xylopyranosyl-(1→2)-*O*-α-rhamnopyranoside (24),[9] mearnsetin-3-*O*-α-L-rhamnopyranoside (25),[30] kaempferol-3-*O*-diglucoside (26), kaempferol-3-*O*-galactoside (27),[15] kaempferol-3-*O*-β-galactopyranoside (28),[35] kaempferol 3-*O*-α-L-arabinopyranoside (29),[30] kaempferol-3-*O*-β-(6”-coumaroyl)-glucopyranoside (30),[9,36] rutin (31),[17] apigenin-7-*O*-glucoside (32),[15] epicatechin (33),[9,35] 5,6,7-trihydroxy-4’-methoxyflavone (34), 5-hydroxy-7,4’-dimethoxy-8-methylflavone (35), 5,7,4’-trihydroxy-6,8-dimethylflavone (36),[28] 4H-1-benzopyran-4-one,5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-6,8-dimethyl (sideroxylin) (37)[39] and 5-hydroxy-4’,7-dimethoxyflavone-(6-C-6”)-5”-hydroxy-3”’,4”’,7”-trimethoxyflavone (38).[9,36]

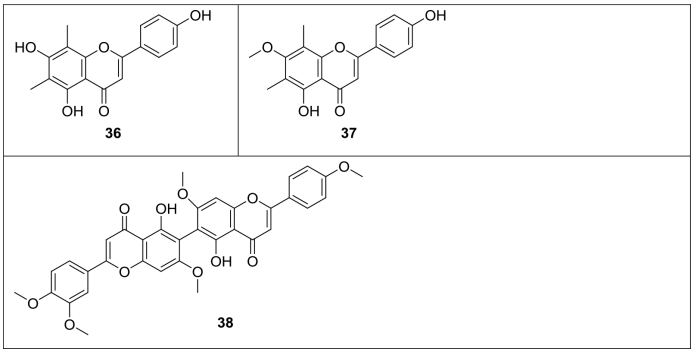
Triterpenes

Amongst the triterpenes isolated from the *Miconia* genus, those of pentacyclic skeleton stand out, especially ursolic acid[39] and oleanolic

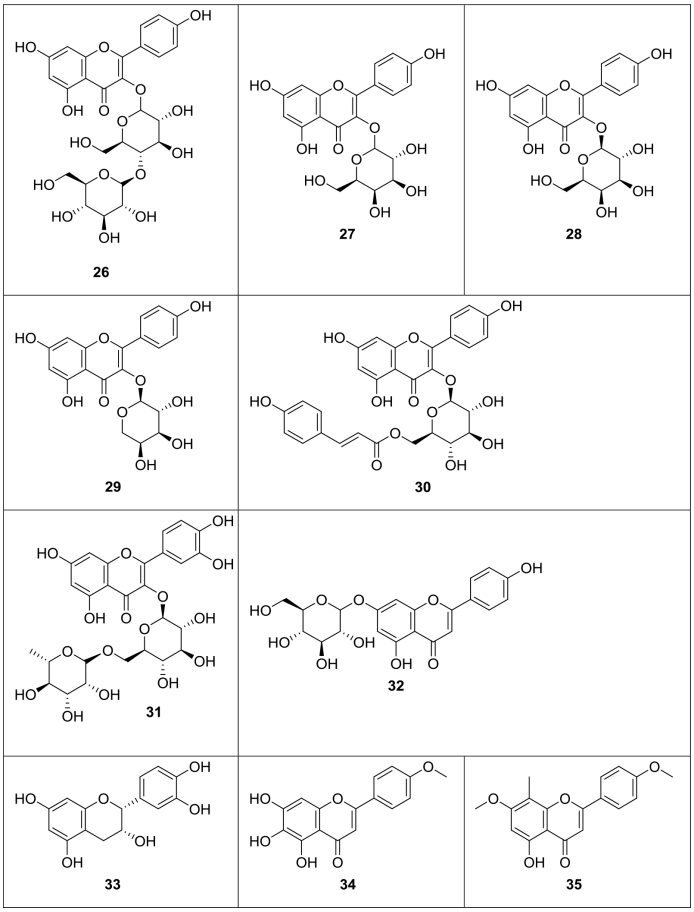


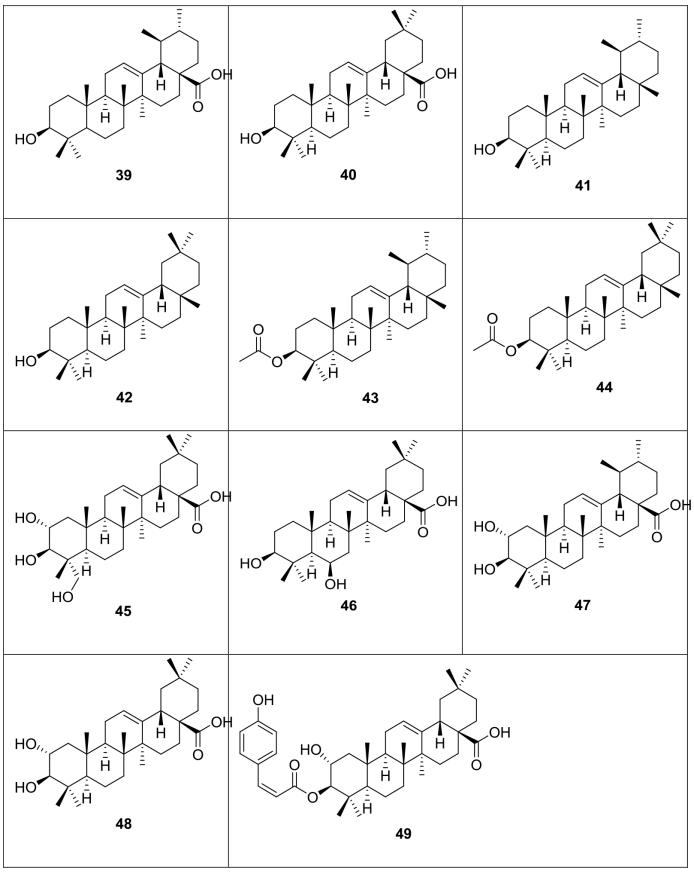


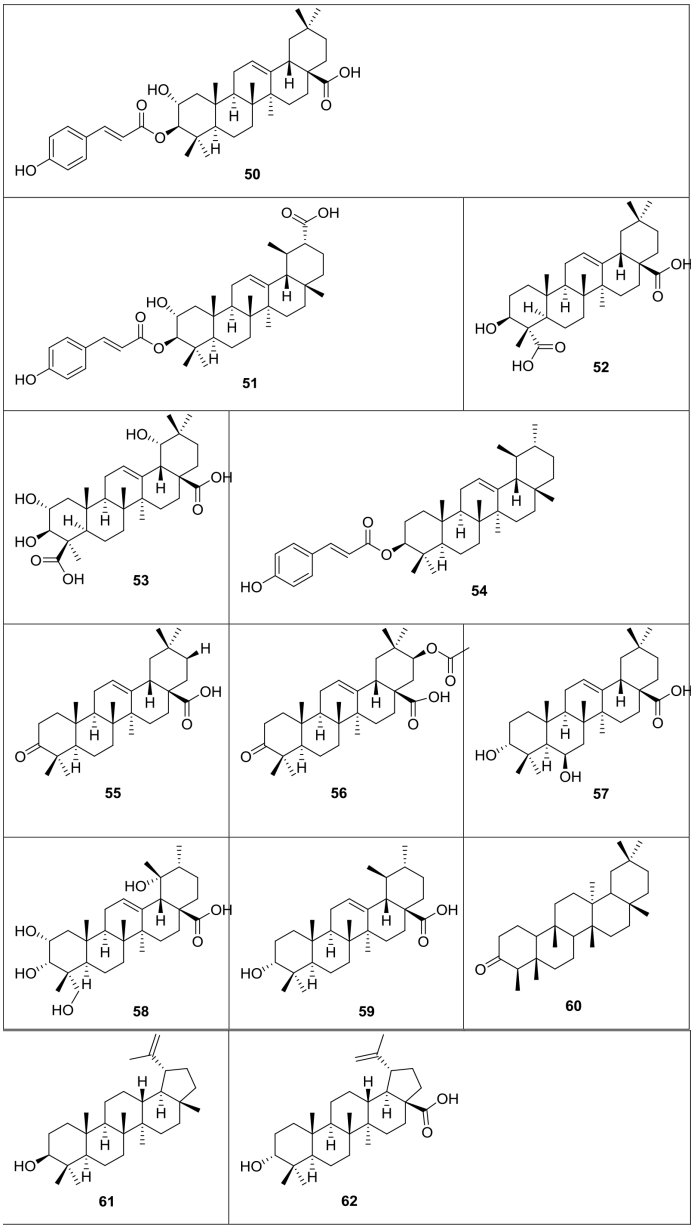


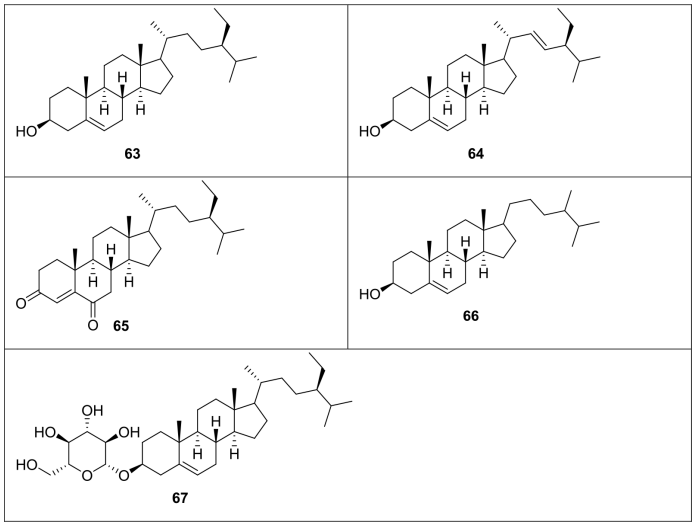


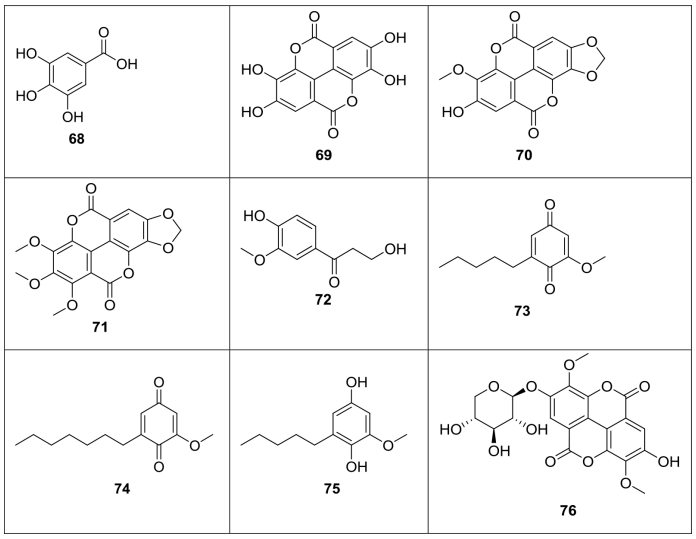
acid[40] which are recurrent in different species such as *M. ferruginata, M. fallax, M. langsdorffii, M. ligustroides, M. sellowiana, M. albicans* and *M. rubiginosa*.[4,8,14,17,18,19,21,23,25,26,28,30,40,41] Other pentacyclic triterpenes and derivatives already isolated from *Miconia* are α-amyrin (41),[17,42] β-amyrin (42), α-amyrin acetate (43), β-amyrin acetate (44),[42] arjunolic acid (45),[6,29,38,40,41] sumaresinolic acid (46),[23,30,43] 2-α-hydroxyursolic acid (47),[40] maslinic acid (48),[30,40] 3-*O*-*cis*-*p*-coumaroyl maslinic acid (49), 3-*O*-*trans*-*p*-coumaroyl maslinic acid (50), 3-*O*-*trans*-*p*-coumaroyl 2α-hydroxydulcioic acid (51),[30] gypsogenic acid (52),[23] 2α,3β,19α-trihydroxyolean-12-ene-24,28-dioic acid (bartogenic acid) (53),[38] 3-(*E*)-*p*-coumaroyl-α-amyrin (54),[17] oleanonic acid (55),[23] 28-carboxy-3-oxoolean-12-en-21α-yl acetate (56),[44] 3-*epi*-sumaresinolic acid (57),[30,43] 2α,3α,19α, 23-tetrahydroxyurs-12-ene-28-oic acid (myrianthic

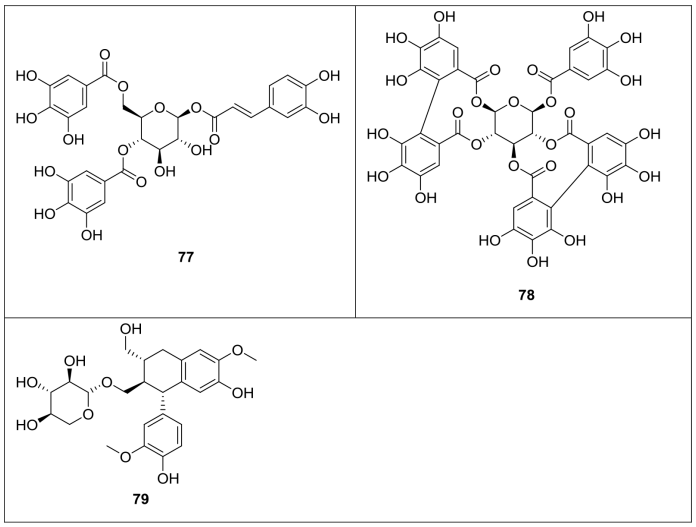












acid) (58),[38] *epi*-ursolic acid (59),[17] friedelin (60), lupeol (61)[42] and *epi*-betulinic acid (62).[17]

Steroids and derivatives

Five steroids and derivatives have been found in *Miconia* genus and these constituents were identified as β-sitosterol (63), stigmasterol (64),[28,42] stigmast-4-ene-3,6-dione (65),[38] campesterol (66)[42] and 3-*O*-β-D-glucopyranosilsitosterol (67).[41]

Other compounds

Besides these compounds mentioned above, there are also other compounds, including phenolic acids, quinones, tannins and lignin reported in *Miconia* genus. These constituents are identified as gallic acid (68),[5,9,35,36] ellagic acid (69),[5] 3'-*O*-methyl-3,4-*O*,*O*-methyleneellagic acid (70), 3',4',5'-tri-*O*-methyl-3,4-*O*,*O*-methyleneflavellagic acid (71), β-hydroxypropiovanillone (72),[29] 2-methoxy-6-pentyl-1,4-benzoquinone (primin) (73),[20,24] 2-methoxy-6-heptyl-1,4-benzoquinone (74),[20] 2-methoxy-6-*n*-pentylhydroquinone (miconidin) (75) (Rosa, 2015),[24] 3,3'-di-*O*-methyl ellagic acid-4-*O*-β-D-xylopyranoside (76),[5] 1-*O*-(*E*)-caffeoyl-4,6-di-*O*-galloyl-β-D-glucopyranose (77),[30] casuarictin (78) and schizandriside (79).[35]

Box 1: Chemical compounds isolated from *Miconia* genus.

Classification	Compound	Structure	Part of plant	Species	References
Flavonoids	quercetin	**(1)**	Leaves	*M. albicans*	[17]
	quercetin-3-*O*-glycoside	**(2)**	Leaves	*M. albicans*	[17]
	quercetin-3-*O*-galactoside	**(3)**	Leaves	*M. alypifolia*	[15]
	quercetin-3-*O*-α-rhamnopyranoside	**(4)**	Leaves	*M. cabucu, M. rubiginosa*	[9,35,36]
	quercetin-3-*O*-β-arabinofuranoside	**(5)**	Leaves	*M. rubiginosa*	[9,35]
	quercetin-3-*O*-α-arabinopyranoside	**(6)**	Leaves	*M. rubiginosa*	[9,35]
	quercetin-3-*O*-β- arabinopyranoside	**(7)**	Leaves	*M. rubiginosa*	[9,35]
	quercetin-3-*O*-β-glucopyranoside	**(8)**	Leaves	*M. cabucu*	[9,36]
	quercetin-3-*O*-β-galactopyranoside	**(9)**	Leaves	*M. rubiginosa*	[9,35]
	quercetin-3-*O*-α-rhamnopyranosyl-(1→4)-*O*-β-galactopyranoside	**(10)**	Leaves	*M. rubiginosa*	[9,35]
	quercetin-3-*O*-(2″-galloyl)-α-*L*-rhamnopyranoside	**(11)**	Leaves	*M. albicans*	[30]
	quercetin-3-*O*-β-xylopiranosyl-(1→2)-*O*-α-rhamnopyranoside	**(12)**	Leaves	*M. cabucu*	[9,36]
	matteucinol	**(13)**	Roots, stems, twigs and leaves	*M. cannabina, M. prasina, M. trailii*	[7,37,38]
	matteucinol 7-*O*-α-L-arabinopyranosyl(1→6)-β-D-glucopyranoside (miconioside A)	**(14)**	Twigs and leaves	*M. trailii*	[38]
	matteucinol 7-*O*-β-D-apiofuranosyl(1→6)-β-D-glucopyranoside	**(15)**	Twigs and leaves	*M. trailii*	[38]
	mattucinol-7-*O*-β-D-glucopyranoside	**(16)**	Twigs and leaves	*M. myriantha*	[5]
	mattucinol-7-*O*-[4”,6”-di-*O*-galloyl]-β-D-glucopyranoside	**(17)**	Twigs and leaves	*M. myriantha*	[5]
	mattucinol-7-*O*-[4”,6”-*O*-(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranoside	**(18)**	Twigs and leaves	*M. myriantha*	[5]
	demethoxymatteucinol	**(19)**	Stems	*M. prasina*	[37]
	7-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyldemethoxymatteucinol (miconioside C)	**(20)**	Stems	*M. prasina*	[37]
	farrerol	**(21)**	Stems	*M. prasina*	[37]
	farrerol 7-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (miconioside B)	**(22)**	Stems, twigs and leaves	*M. prasina, M. trailii*	[37,38]
	myricetin-3-*O*-α-rhamnopyranoside	**(23)**	Leaves	*M. cabucu, M. albicans*	[9,30,36]
	myricetin-3-*O*-β-xylopyranosyl-(1→2)-*O*-α-rhamnopyranoside	**(24)**	Leaves	*M. cabucu*	[9]
	mearnsetin-3-*O*-α-L-rhamnopyranoside	**(25)**	Leaves	*M. albicans*	[30]
	kaempferol-3-*O*-diglucoside	**(26)**	Leaves	*M. alypifolia*	[15]
	kaempferol-3-*O*-galactoside	**(27)**	Leaves	*M. alypifolia*	[15]
	kaempferol-3-*O*-β-galactopyranoside	**(28)**	Leaves	*M. rubiginosa*	[35]
	kaempferol 3-*O*-α-L-arabinopyranoside	**(29)**	Leaves	*M. albicans*	[30]
	kaempferol-3-*O*-β-(6”-coumaroyl)-glucopyranoside	**(30)**	Leaves	*M. cabucu*	[9,36]
	rutin	**(31)**	Leaves	*M. albicans*	[17]
	apigenin-7-*O*-glucoside	**(32)**	Leaves	*M. alypifolia*	[15]
	epicatechin	**(33)**	Leaves	*M. rubiginosa*	[9,35]
	5,6,7-trihydroxy-4’-methoxyflavone	**(34)**	Leaves	*M. ferruginata*	[28]
	5-hydroxy-7,4’-dimethoxy-8-methilflavone	**(35)**	Leaves	*M. ferruginata*	[28]
	5,7,4’-trihydroxy-6,8-dimethilflavone	**(36)**	Leaves	*M. ferruginata*	[28]
	4H-1-benzopyran-4-one,5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-6,8-dimethyl (sideroxylin)	**(37)**	Leaves	*M. ioneura*	[39]
	5-hydroxy-4’,7-dimethoxyflavone-(6-C-6”)-5”-hydroxy-3”’,4”’,7”-trimethoxyflavone	**(38)**	Leaves	*M. cabucu*	[9,36]

continued...

Box 1: Cont'd.

Triterpenes	ursolic acid	**(39)**	Aerial parts, leaves, wood	*M. albicans, M. fallax, M. ligustroides, M. sellowiana, M. langsdorffii, M. ferruginata, M. rubiginosa*	[4,8,14,17-19,25,26,28,30,40,41]
	oleanolic acid	**(40)**	Leaves, aerial parts, wood	*M. ferruginata, M. langsdorffii, M. ligustroides, M. fallax, M. albicans, M. rubiginosa*	[4,8,14,18,19,21,23,25,26,28,30,40,41]
	α-amyrin	**(41)**	Aerial parts, leaves	*M. albicans, M. pepericarpa, M. sellowiana, M. falax, M. rubiginosa, M. ligustroides*	[17,42]
	β-amyrin	**(42)**	Aerial parts	*M. albicans, M. pepericarpa, M. sellowiana, M. falax, M. rubiginosa, M. ligustroides*	[42]
	α-amyrin acetate	**(43)**	Aerial parts	*M. rubiginosa*	[42]
	β-amyrin acetate	**(44)**	Aerial parts	*M. rubiginosa*	[42]
	arjunolic acid	**(45)**	Aerial parts, wood, stems, roots	*M. ligustroides, M. trailii, M. albicans M. affinis, M. pilgeriana*	[6,29,38,40,41]
	sumaresinolic acid	**(46)**	Aerial parts, leaves	*M. stenostachya, M. albicans, M. fallax*	[23,30,43]
	2-α-hydroxyursolic acid	**(47)**	Aerial parts	*M. sellowiana*	[40]
	maslinic acid	**(48)**	Aerial parts, leaves	*M. sellowiana, M. albicans*	[30,40]
	3-*O*-*cis*-*p*-coumaroyl maslinic acid	**(49)**	Leaves	*M. albicans*	[30]
	3-*O*-*trans*-*p*-coumaroyl maslinic acid	**(50)**	Leaves	*M. albicans*	[30]
	3-*O*-*trans*-*p*-coumaroyl 2α-hydroxydulcioic acid	**(51)**	Leaves	*M. albicans*	[30]
	gypsogenic acid	**(52)**	Aerial parts	*M. stenostachya*	[23]
	2α,3β,19α-trihydroxyolean-12-ene-24,28-dioic acid (bartogenic acid)	**(53)**	Twigs and leaves	*M. trailii*	[38]
	3-(*E*)-*p*-coumaroyl-α-amyrin	**(54)**	Leaves	*M. albicans*	[17]
	oleanonic acid	**(55)**	Aerial parts	*M. fallax*	[23]
	28-carboxy-3-oxoolean-12-en-21α-yl acetate	**(56)**	Leaves	*M. macrothyrsa*	[44]
	3-*epi*-sumaresinolic acid	**(57)**	Leaves	*M. albicans, M. stenostachya*	[30,43]
	2α,3α,19α, 23-tetrahydroxyurs-12-ene-28-oic acid (myrianthic acid)	**(58)**	Twigs and leaves	*M. trailii*	[38]
	epi-ursolic acid	**(59)**	Leaves	*M. albicans*	[17]
	friedelin	**(60)**	Aerial parts	*M. rubiginosa*	[42]
	lupeol	**(61)**	Aerial parts	*M. albicans, M. pepericarpa, M. sellowiana, M. falax, M. ligustroides*	[42]
	epi-betulinic acid	**(62)**	Leaves	*M. albicans*	[17]
Steroids	β-sitosterol	**(63)**	Leaves and aerial parts	*M. ferruginata, M. albicans, M. pepericarpa, M. sellowiana, M. falax, M. rubiginosa, M. ligustroide*	[28,42]
	stigmasterol	**(64)**	Leaves and aerial parts	*M. ferruginata, M. albicans, M. pepericarpa, M. sellowiana, M. falax, M. rubiginosa*	[28,42]
	stigmast-4-ene-3,6-dione	**(65)**	Twigs and leaves	*M. trailii*	[38]
	campesterol	**(66)**	Aerial parts	*M. albicans, M. pepericarpa, M. sellowiana*	[42]
	3-*O*-β-D-glucopyranosilsitosterol	**(67)**	Wood	*M. albicans*	[41]

continued...

Box 1: Cont'd.

Others	gallic acid	**(68)**	Twigs and leaves	*M. myriantha, M. cabucu, M. rubiginosa*	[5,9,35,36]
	ellagic acid	**(69)**	Twigs and leaves	*M. myriantha*	[5]
	3'-*O*-methil-3,4-*O*,*O*-methyleneellagic acid	**(70)**	Stems	*M. affinis*	[29]
	3',4',5'-tri-*O*-methyl-3,4-*O*,*O*-methyleneflavellagic acid	**(71)**	Stems	*M. affinis*	[29]
	β-hydroxypropiovanillone	**(72)**	Stems	*M. affinis*	[29]
	2-methoxy-6-pentyl-1,4-benzoquinone (primin)	**(73)**	Leaves, aerial parts	*M. lepidota, M. willdenowii*	[20,24]
	2-methoxy-6-heptyl-1,4-benzoquinone	**(74)**	Leaves	*M. lepidota*	[20]
	2-mehtoxy-6-*n*-pentylhydroquinone (miconidin)	**(75)**	Aerial parts	*M. willdenowii*	[24]
	3,3'-di-*O*-methyl ellagic acid-4-*O*-β-D-xylopyranoside	**(76)**	Twigs and leaves	*M. myriantha*	[5]
	1-*O*-(*E*)-caffeoyl-4,6-di-*O*-galloyl-β-D-glucopyranose	**(77)**	Leaves	*M. albicans*	[30]
	casuarictin	**(78)**	Leaves	*M. rubiginosa*	[35]
	schizandriside	**(79)**	Leaves	*M. rubiginosa*	[35]

Biological activities

Previous investigations have considered the biological activities of extracts obtained from *Miconia* and their isolated compounds and reported that species of this genus possesses various pharmacological activities including antimicrobial, trypanocidal, antileishmanial, schistosomicidal, antimalarial, insecticidal, antitumor, antioxidant, antidiabetic, analgesic and anti-inflammatory effects (Box 2).

Antimicrobial effect

Miles *et al.* (1991)[7] evaluated the antibacterial, antifungal and antifeedant active constituents from Peruvian plants. This study found that the ethanolic extract obtained from the roots of *Miconia cannabina* revealed the highest antifungal activity when tested against *Pythium ultimum*, *Rhizoctonia solani* and *Helminthosporium teres* using the preliminary "paper disc" method. From this extract was isolated the flavonoid matteucinol (13) that demonstrated excellent antifungal activity against *R. solani* (135% relative activity).

Arjunolic acid (45), a triterpene isolated from from the ethanol extract of the roots of *Miconia pilgeriana* showed moderate activity against the enzyme fatty acid synthase (FAS), a potential antifungal target, with IC_{50} value of 27.5 μg/ml. To establish the correlation of FAS inhibitory effects and antifungal activity, arjunolic acid, as well as other compounds, was evaluated for their antifungal activity against *Candida albicans* and *Cryptococcus neoformans*. However, the results indicated that compounds with relatively higher FAS inhibitory activity did not exhibit antifungal activity against the above two pathogens. Based on the results, the authors could conclude that FAS inhibition is not directly correlated to antifungal activity, at least for the chemotypes examined in the study.[6]

Activity-guided fractionation of an ethanol extract of twigs and leaves of *Miconia myriantha* for *Candida albicans* secreted aspartic proteases (SAP) inhibition resulted in the identification of four phenolic compounds. Of these compounds, mattucinol-7-O-[4'',6''-*O*-(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranoside (18) and ellagic acid (69) showed inhibitory effects against *Candida albicans* SAP, with IC_{50} of 8.4 and 10.5 μM, respectively.[5]

Celotto *et al.* (2003)[3] evaluated the antimicrobial activity of crude extracts of three *Miconia* species (*M. albicans*, *M. rubiginosa* and *M. stenostachya*) against eleven selected micro-organisms, including Gram-positive, Gram-negative bacteria and a yeast species. Results showed that ethanol extracts of *M. albicans* and *M. rubiginosa* were the most active, inhibiting the growth of *Staphylococus aureus, Staphylococus saprophyticus, Streptococus agalactiae, Shigella flexneri, Klebsiella pneumonia* and *Candida albicans*. On the other hand, that ethanol extract of *M. rubiginosa* was active only against *C. albicans*.

Later, Rodrigues *et al.* (2008)[9] assessed the effects of the methanol and chloroform extracts of the leaves of *Miconia cabucu*, *Miconia rubiginosa* and *Miconia stenostachya* on the inhibition of the growth of *Staphylococcus epidermidis, Candida albicans, Staphylococcus aureus, Micrococcus luteus, Enterococcus faecalis, Bacillus subtilis, Bacillus cereus, Escherichia coli* and *Salmonella*. The results obtained showed that the methanol extracts of the leaves of *M. rubiginosa* and *M. stenostachya* and the chloroform extract of the leaves of *M. cabucu* presented antimicrobial activity against the tested micro-organisms. The phytochemical study of these extracts revealed the presence of triterpenes and hydrocarbons in chloroform extracts and the presence of flavonoids in the methanol extracts from *M. rubiginosa* and *M. stenostachya*, suggesting that these compounds might be responsible for the antimicrobial activity.

Corrupting the antimicrobial activity of *M. rubiginosa*, Queiroz *et al.* (2011)[8] points that the ethanolic and dichloromethane extracts from the aerial parts of this plant where shown to exhibit activity against *E. faecalis, K. rhizophila, E. coli, P. aeruginosa and S. choleraesuis*, but the two isolated compounds, ursolic acid (39) and oleanolic acid (40), are not active against the tested bacterial.

Triterpene acids isolated from *Miconia* species (*M. fallax, M. albicans, M. stenostachya* and *M. sellowiana*) along with a mixture of that triterpenes, as well as semi-synthetic derivatives, were evaluated against *Streptococcus mutans, Streptococcus mitis, Streptococcus sanguinis, Streptococcus salivarius, Streptococcus sobrinus and Enterococcus faecalis*, which are potentially responsible for the formation of dental caries in humans. The triterpenes ursolic (39), oleanolic (40), gypsogenic (52) and sumaresinolic (46) acids, along with a mixture of ursolic and oleanolic acids and a mixture of maslinic (48) and 2-α-hydroxyursolic (47) acids, as well as ursolic acid derivatives displayed activity against all the tested bacteria, showing that they are promising antiplaque and anticaries agents.[10]

The methylene chloride extract of *Miconia ligustroides*, the isolated compounds ursolic (39) and oleanolic (40) acids and a mixture of these

Box 2: Biological activities observed in *Miconia* genus.

Specie	Part of plant	Biological Activities	References
M. affinis	Stems	Fungicidal activity against *M. oryzae* and *S. tritici*.	[29]
M. albicans	Leaves, aerial parts	Antioxidant activity. f Antidiabetic properties. Analgesic activity. Analgesic and anti-inflamatory activities. Antibacterial activity against *S. mutans, S. mitis, S. sanguinis, S. salivarius, S. sobrinus* and *E. faecalis* Cytotoxic and antimutagenic activity. Antimicrobial activity against *S. aureus, S. saprophyticus, S. agalactiae, S. flexneri, K. pneumonia* and *C. albicans*.	[10,13,17,22,30]
M. alypifolia	Leaves	Antioxidant activity.	[15]
M. cabucu	Leaves, aerial parts	Antimicrobial activity against *S. epidermidis, C. albicans* and *S. aureus*. Cytotoxic and antimutagenic activity.	[9,22]
M. cannabina	Roots	Antifungal activity against *R. solani*.	[7]
M. fallax	Aerial parts	Antimutagenic activity. Antitumor activity against cells of the human uterine cervix adenocarcinoma. Trypanocidal activity against blood trypomastigote forms of *T. cruzi*. Protective effect against colon carcinogenesis. Antibacterial activity against *S. mutans, S. mitis, S. sanguinis, S. salivarius, S. sobrinus* and *E. faecalis*.	[10,18,19,21,23]
M. ferruginata	Leaves	Insecticidal activity against *S. frugiperda*.	[28]
M. ioneura	Leaves	Antimicrobial activity against *C. krusei, C. guillermondii* and *C. albicans*.	[39]
M. langsdorffii	Aerial parts	Antileishmanial activity against the promastigote forms of *L. amazonensis*. Schistosomicidal activity against *S. mansoni*.	[25,26]
M. lepidota	Leaves	Cytotoxicity and anticancer activity.	[20]
M. lehmannii	Aerial parts	Antioxidant activity.	[16]
M. ligustroides	Aerial parts	Trypanocidal activity against trypomastigotes forms of *T. cruzi*. Antimicrobial activity against *B. cereus, V. cholerae, S. choleraesuis, K. pneumoniae* and *S. pneumonia*.	[4,40]
M. myriantha	Twigs and leaves	Antifungal activity against *C. albicans*.	[5]
M. nervosa	Leves	Antimalarial activity against *P. falciparum* K1 strain.	[27]
M. pilgeriana	Roots	Fatty acid synthase inhibitory effects.	[6]
M. salicifolia	Not informed	Antibacterial activity against *E. coli* and *S. aureus.*	[45]
M. sellowiana	Aerial parts	Trypanocidal activity against trypomastigotes forms of *T. cruzi*. Antibacterial activity against *S. mutans, S. mitis, S. sanguinis, S. salivarius, S. sobrinus* and *E. faecalis*. Antimicrobial activity against S. *epidermidis, C. albicans, S. aureus, M. luteus, B. subtilis* and *B. cereus*.	[10,40]
M. stenostachya	Leaves, aerial parts	Trypanocidal activity against blood trypomastigote forms of *T. cruzi*. Antibacterial activity against *S. mutans, S. mitis, S. sanguinis, S. salivarius, S. sobrinus* and *E. faecalis*. Cytotoxic and antimutagenic activity. Antimicrobial activity against *C. albicans.*	[9,10,22,23]
M. rubiginosa	Leaves, aerial parts	Antimicrobial activity against *E. faecalis, K. rhizophila, E. coli, P. aeruginosa* and *S. choleraesuis.* Antimicrobial activity against *S. epidermidis, C. albicans, S. aureus, M. luteus, B. subtilis* and *B. cereus*. Cytotoxic and antimutagenic activity. Antimicrobial activity against *S. aureus, S. saprophyticus, S. agalactiae, S. flexneri, K. pneumonia* and *C. albicans*. Analgesic activity.	[8,9,12,22]
M. willdenowii	Leaves	Trypanocidal activity against epimastigote form of *T. cruzi*.	[24]

triterpenes and ursolic acid derivatives were evaluated against *Bacillus cereus*, *Vibrio cholerae*, *Salmonella choleraesuis*, *Klebsiella pneumoniae* and *Streptococcus pneumonia*. The methylene chloride extract showed no activity against the selected micro-organisms. Ursolic acid was active against *B. cereus* and oleanolic acid was effective against *B. cereus* and *S. pneumonia*. The mixture of triterpenes did not enhance the antimicrobial activity. However, the acetyl and methyl ester derivatives, prepared from ursolic acid, increased the inhibitory activity for *S. pneumonia*.[4]

In 2010, Bussmann *et al.* (2010)[45] evaluate the minimum inhibitory concentration of ethanolic and water extracts of 141 plant species used in Northern Peru to treat bacterial infections. *Miconia salicifolia* ethanolic extract exhibited high activity against *Staphylococcus aureus* (MIC = 0.0625 mg/ml).

Tracanna *et al*. (2010)[39] evaluated the antimicrobial activity of the ethyl acetate extract of leaves of *Miconia ioneura* and the flavone sideroxylin (37) isolated from this extract. The extract and the flavone were screened for antifungal activity using several *Candida* strains and the more potent antifungal activity of both extract and sideroxylin were against *C. krusei*, followed by *C. guillermondii* and *C. albicans*. The authors point out that the flavone is the main responsible of biological activity presented by the ethyl acetate extract, since the anti-fungical activity observed by the two is very similar.

Trypanocidal effect

In a study by Cunha *et al*. (2003b),[23] the trypanocidal activity of triterpenes isolated from the methylene chloride extracts of aerial parts of *Miconia fallax* and *Miconia stenostachya* was evaluated. Ursolic (39), oleanolic (40) and gypsogenic (52) acids were active against blood trypomastigote forms of *Trypanossoma cruzi*, while sumaresinolic (46) and oleanonic (55) acids and the methyl and acetyl ester derivatives of the mixture of ursolic and oleanolic triterpenes were inactive. These results suggest the importance of polar groups for trypanocidal activity.

From methylene chloride extracts of aerial parts of *Miconia sellowiana* and *Miconia ligustroides* were isolated the triterpenes ursolic (39), arjunolic (45) and oleanolic (40) acids along with a mixture of 2 α-hydroxyursolic acid (47) and maslinic acid (48) and their activities against the trypomastigote blood forms of *Trypanosoma cruzi* were evaluated.[40] The results corroborate the suggestion presented by the group in 2003,[23] since the assays showed that ursolic acid, oleanolic acid and the potassium salt derivative of ursolic acid were the most active. In contrast, a mixture of 2 α-hydroxyursolic acid and maslinic acid was much less potent than a mixture of that ursolic and oleanolic acids. In the same manner, arjunolic acid displayed weak trypanocidal activity when compared with the other triterpenes.

Later, Rosa (2015) [24] evaluated the trypanocidal activity of some extracts of 10 species of Brazilian plants, including *Miconia lepidota*. The extracts were tested *in vitro* against cultures epimastigotes of *Trypanosoma cruzi*. In the case of *M. lepidota*, the extract that showed activity was ethanolic, obtained from aerial parts as well as the fraction ethyl acetate, from which two hydroquinones derivatives were isolated: miconidin (75) and primin (73). The anti *T. cruzi* bioassay, when performed to the isolated compounds, allowed observing higher trypanocidal potential than the reference drug (benznidazole).

Antileishmanial effect

Peixoto *et al.* (2011)[25] evaluated the *in vitro* activity of the crude hydroalcoholic extract of the aerial parts of *Miconia langsdorffii* against the promastigote forms of *Leishmania amazonensis*, the causative agent of cutaneous leishmaniasis in humans. The fractionation of this extract led to identification of the triterpenes ursolic (39) and oleanolic (40) acids as the major compounds in the fraction that displayed the highest activity. These compounds gave IC_{50} values of 360.3 μM and 439.5 μM, respectively. In addition, a mixture of the triterpenes displayed increased antileishmanial activity, with an IC_{50} of 199.6 μM.

Schistosomicidal effect

Results obtained by Cunha *et al.* (2012)[26] indicated that crude extracts and fractions of aerial parts of *Miconia langsdorffii* and others Brazilian Cerrado species were able to induce worm death in the *in vitro* schistosomicidal assay against *Schistosoma mansoni*. On the first day of incubation, crude extract of *M. langsdorffii* at a concentration of 100 μg/ml caused 25% adult worms mortality and on the fifth day of incubation 100% parasite mortality was achieved with this extract at concentration of 100 μg/ml.

Antimalarial effect

Sixty-nine extracts from eleven plant species, including *M. nervosa*, were prepared and screened for *in vitro* activity against *Plasmodium falciparum* K1 strain and for cytotoxicity against human fibroblasts and two melanoma cell lines. High *in vitro* antiplasmodial activity was observed for *M. nervosa* leaf methanol extracts (IC_{50} = 9.9 μg/ml) and moderate activity was observed for *M. nervosa* bark and leaf chloroform extracts and leaf decoction. *M. nervosa* bark decoction and methanolic extracts were inactive *in vitro* against *P. falciparum*.[27]

Insecticidal effect

In 2014, a library of 600 taxonomically diverse Panamanian plant extracts, including *Miconia affinis* extract, was screened for fungicidal, insecticidal and herbicidal activities and the ethyl acetate extract of *M. affinis* showed one fraction active against *Magnaporthe oryzae* and *Septoria tritici*. Of this fraction was isolated, among other compounds, arjunolic acid (45), which showed good fungicidal activity against *M. oryzae* and *S. tritici*.[29]

Recently, Cunha *et al.* (2017)[28] describes the insecticidal effects of leaf extracts of *Miconia ferruginata* against the fall armyworm (*Spodoptera frugiperda*), to one of the main pests of maize. They found that the ethanolic extract of leaves of *M. ferruginata* presenting larval mortality (56.67%) and showed an elongation of the larval stage of 16.56 days as compared to the control. A pupal stage is also affected, showing a stretching of 8.49 days in relation to the control.

Antitumor effect

In 2001, Gunatilaka *et al*. (2001)[20] reported that benzoquinones isolated from the leaves of *Miconia lepidota* exhibited activity toward mutant yeast strains based on *Saccharomyces cerevisiae*, indicative of their cytotoxicity and potential anticancer activity. These quinones were tested in two cytotoxicity assays. In the M109 tumor cell lines, quinones had an IC_{50} value of 10 μg/ml. In the A2780 cell line, 2-methoxy-6-heptyl-1,4-benzoquinone (74) and 2-methoxy-6-pentyl-1,4-benzoquinone (primin) (73) had IC_{50} values of 7.9 and 2.9 μg/ml, respectively.

Results obtained by Resende *et al.* (2006)[21] support the indication of triterpenes ursolic (39) and oleanolic (40) acids as promising candidates in the prevention of cancer. In this study, ursolic and oleanolic acids isolated from the aerial parts of *Miconia fallax* were evaluated for antimutagenic potential using the micronucleus test in peripheral blood and bone marrow of Balb/c mice and the results showed a significant reduction on micronucleus frequency in the groups concomitantly treated with the triterpenes and doxorubicin, a antineoplastic agent, compared to that treated with doxorubicin alone.

Cunha *et al.* (2008)[18] also evaluated the antitumor potential of *M. fallax* specie. In this study, *in vitro* tumor growth inhibition by the ethanol extract of the aerial parts of *M. fallax* was evaluated in culture media containing cells of the human uterine cervix adenocarcinoma cell line, HeLa. Bioassay-guided fractionation of this extract furnished a mixture

of ursolic (39) and oleanolic (40) acids. Both the ethanol extract and the mixture of the triterpenes produced dose-dependent tumor growth inhibition.

Additionally, ursolic (39) and oleanolic (40) acids isolated from the methylene chloride extract of aerial parts of *M. fallax* were also reported to have a protective effect against colon carcinogenesis.[19]

Serpeloni *et al*. (2011)[22] evaluated the cytotoxicity, mutagenicity and the protective effects of methanolic extracts from the aerial parts of *Miconia cabucu*, *Miconia rubiginosa*, *Miconia stenostachya* and *Miconia albicans*. The results reinforce the protective effects on doxorubicin-induced mutagenicity.

Antioxidant effect

Mancini *et al*. (2008)[15] isolated four flavonoids of methanolic extract of leaves of *Miconia alypifolia* and evaluated the antioxidant activity of these compounds. The antioxidant potentials of compounds were measured by ABTS (2,2'-azinobis (3-ethylbenzothiozoline-6-sulfonate) radical cation (ABTS•+) scavenging test. At 30 μM concentration of each compound, the order of potency of isolated flavonoids were kaempferol-3-*O*-diglucoside (26) > quercetin-3-*O*-galactoside (3) > apigenin-7-*O*-glucoside (32) > kaempferol-3-*O*-galactoside (27).

In 2009, Mosquera, Correra and Niño (2009)[16] analyzed the antioxidant activity of forty-six methanol plant extracts from Colombian flora, including *Miconia aeruginosa*, *Miconia lehmannii* and *Miconia quintuplinervia*. *M. lehmannii* presented 45.3% of antioxidant activity.

In addition, the antioxidant effects of phenolic compounds were also demonstrated in the studies by Pieroni *et al*. (2011).[17] The results with antioxidant assays showed that the methanolic extract of *Miconia albicans* leaves, the n-butanolic fraction and the isolated flavonoids had a significant scavenging capacity against AAPH and DPPH.

Antidiabetic effect

Lima *et al*. (2018)[30] evaluated the ethyl acetate extract of leaves of *Miconia albicans* by high-resolution protein tyrosine kinase 1B (PTP1B) inhibition profiling for identification of antidiabetic compounds. In this study, five flavonoids and eight triterpenoid PTP1B inhibitors were identified. These results support the use of *M. albicans* as a traditional medicine with antidiabetic properties.

Analgesic and anti-inflammatory effect

The analgesic effects of the hexane, methylene chloride and ethanol extracts of *Miconia rubiginosa* and *Miconia albicans* were evaluated by Spessoto *et al*. (2003)[12] and Vasconcelos *et al*. (2003),[13] respectively. The extracts of *M. rubiginosa* produced a significant inhibition of acetic acid-induced abdominal writhing and showed a significant antinociceptive effect.[12] The extracts in hexane and methylene chloride of *M. albicans* produced significant antinociception in the writhing test. On the other hand, none of the extracts of *M. albicans* had a significant effect on the hot plate test.[13]

In 2006, Vasconcelos *et al*. (2006)[14] used *in vivo* models to evaluate the analgesic and anti-inflammatory activities of ursolic (39) and oleanolic (40) acids, the main constituents of the methylene chloride extract of *M. albicans*, in an attempt to clarify if these compounds are responsible for the analgesic properties displayed by this extract. In the abdominal constriction test, the oral administration of both triterpenes showed a dose-dependent inhibition of acetic acid-induced abdominal writhes in mice. In the case of the carrageenan-induced paw oedema test in rats, the oral administration of triterpenes led to a significant anti-oedematous effect. In addition, both acids reduced the number of paw licks in the second phase of the formalin test.

A significant analgesic effect was observed after oral administration to mice of the extracts in hexane, methylene chloride and ethanol of aerial parts of *Miconia ligustroides*, suggesting that they were efficient in increasing the pain threshold.[11]

CONCLUSION

Despite being one of the most representative genus from the Melastomataceae family, *Miconia* still presents few studies regarding its phytochemicals and biological activities. Although above 1050 species of *Miconia* are distributed all over the world, only a few of them have been investigated so far. From our review, it can be concluded that phytochemical and pharmacological investigations mainly focused on *M. albicans*, *M. fallax*, *M. sellowiana*, *M. stenostachya* and *M. rubiginosa*. Researches have concentrated mainly on aerial parts of plants. Therefore, future phytochemistry and pharmacological researches could be focused on the other parts of plants already mentioned in the literature, as well as advance in the study of new species of the genus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

IC_{50}: Inhibitory Concentration 50; **MIC:** Minimum Inhibitory Concentration; ***M. stenostachya:*** *Miconia stenostachya;* ***M. albicans:*** *Miconia albicans;* ***M. pepericarpa:*** *Miconia pepericarpa;* ***M. sellowiana:*** *Miconia sellowiana;* ***M. fallax:*** *Miconia fallax;* ***M. rubiginosa:*** *Miconia rubiginosa;* ***M. ligustroides:*** *Miconia ligustroides;* ***M. ferruginata:*** *Miconia ferruginata;* ***M. langsdorffii:*** *Miconia langsdorffii;* ***M. macrothyrsa:*** *Miconia macrothyrsa;* ***M. affinis:*** *Miconia affinis;* ***M. lepidota:*** *Miconia lepidota;* ***M. pilgeriana:*** *Miconia pilgeriana;* ***M. myriantha:*** *Miconia myriantha;* ***M. alypifolia:*** *Miconia alypifolia;* ***M. cannabina:*** *Miconia cannabina;* ***M. cabucu:*** *Miconia cabucu;* ***M. willdenowii:*** *Miconia willdenowii;* ***M. prasina:*** *Miconia prasina;* ***M. ioneura:*** *Miconia ioneura;* ***M. trailii:*** *Miconia trailii;* ***R. solani:*** *Rhizoctonia solani;* ***C. albicans:*** *Candida albicans;* ***B. cereus:*** *Bacillus cereus;* ***S. pneumonia:*** *Streptococcus pneumonia;* ***C. krusei*:** *Candida krusei;* ***C. guillermondii:*** *Candida guillermondii;* ***T. cruzi*:** *Trypanosoma cruzi;* ***P. falciparum:*** *Plasmodium falciparum;* ***M. oryzae*:** *Magnaporthe oryzae*; ***S. tritici:*** *Septoria tritici.*

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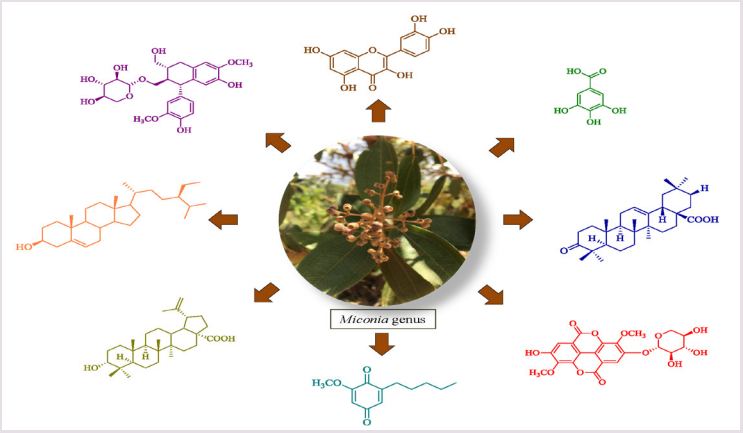
GRAPHICAL ABSTRACT



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