Pharmacogn. Rev.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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REVIEW ARTICLE

Pharmacology of *Mikania* genus: A Systematic Review

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ABSTRACT

Genus *Mikania*, in which "guaco" species are included, encloses many species of pharmaceutical interest that are well distributed throughout South America. This work aims to make a systematic review of the clinical and nonclinical data already published about some *Mikania* species and their existing products, available in the pharmaceutical market. As usual, some species are more studied than others and the most studied species to date are *Mikania glomerata, Mikania laevigata, Mikania scandens,* and *Mikania micrantha*. The first two are widely used in Brazil to treat respiratory disorders and are available in different preparations marketed in retail pharmaceutical stores. Among the reported activities, anti-inflammatory, analgesic, antibacterial, and central nervous system activities were the most tested since they are directly related to the popular use of some species of this genus. In addition, a noteworthy amount of toxicological studies in animals are published in the literature. Thus, this systematic review aims to gather knowledge about *Mikania* genus and consequently to contribute for a safer use of derivatives of its species.

Key words: *Asteraceae,* medicinal plants, pharmacological effects, phytotherapy

INTRODUCTION

The World Health Organization (WHO), in 2013, elaborated the strategies aiming the official implantation of integrative and complementary practices (ICPs), which include phytotherapy (complementary traditional medicine), in the health system of WHO-members countries from different continents, from different ethnic and cultural origins, and where different ICPs are officialized, either financed by health insurance system, or inserted in public policies that mobilize important portions of each population, like practitioners or patients of the complementary traditional medicine. It is noteworthy to point that a complementary traditional medicine of quality, safety, and effectiveness contributes to the broad universal access to health care.[1]

Moreover, in the last decades, the use of medicinal plants has increased substantially, either as remedies used in the traditional medicine[2,3] or as a material for producing dietary supplements, both in Western world and Asia. Despite the extensive development of pharmaceutical synthesis methods, medicinal plants still represent important sources of new products, mainly because plants can synthesize and produce constituents that are structurally too complex to be obtained through chemical synthesis.[3]

In the context of the phytotherapy, different botanical families contribute with many genus and, considering the genera from *Asteraceae* family, *Mikania* presents some species, popularly known as "guaco," which have been widely used in Brazil due to their therapeutic properties. Species such as *Mikania glomerata* and *Mikania laevigata* are widely used to treat respiratory diseases on the basis of their antitussive, expectorant, and bronchodilator activities,[4] in the form of phytomedicines, either as magistral or officinal formulations.[5]

Mikania genus belongs to *Asteraceae* family, which includes about 22,800 species already described,[6] some of them are widely used in folk medicine. Approximately, 450 *Mikania* species are mainly distributed in the American tropical and temperate regions. In Brazil, 203 species are found.[7]

In South America, there are two major diversity centers of the genus; one located in Brazil, between Minas Gerais, Rio de Janeiro, Paraná, and Santa Catarina States, comprising approximately 170 species. There are also many species occurring in Paraguay, Uruguay, and Argentina. The other distribution center, with approximately 150 species, is in the Andean countries, from Colombia to Bolivia. A small number of *Mikania* species, one of the few *Asteraceae* genera that develops in the lowlands of the Amazon region, is found outside these centers, since this region is considered inadequate for most of the members of this family.[8]

Mikania species have acknowledged therapeutic importance since they show different pharmacological activities, according to the literature.[9] The therapeutic activities are highlighted as that on respiratory tract, anti-inflammatory,[10-15] anti-allergic, analgesic,[16] antioxidant,[17] as well on the central nervous system (CNS)[18] and antimicrobial.[19]

The quantification of active substances present in medicinal plants is a way for guaranteeing the quality of their derivatives used in phytotherapeutical practice. In this sense, metabolites of different classes have already been isolated from *Mikania* species, which are usually associated with their pharmacological activities, the main ones are coumarin, o-coumaric acid, kaurenoic acid, cinnamoylgrandifloric acid, syringaldehyde, and

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Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/phrev.phrev_10_18

Cite this article as: da Silva AS, Owiti AO, Barbosa WLR. Pharmacology of *Mikania* genus: A systematic review. Phcog Rev 2018;12:230-7.

stigmasterol or metabolic classes such as triterpenes/steroids, flavonoids, sesquiterpenes and lactones, saponins, and tannins. Caffeine derivatives among other substances have already been found in fewer amounts. In addition, other analyses revealed the presence of alcohols, acids, esters, aldehydes, and organic esters in *Mikania* species.[20]

Medicinal plants are subject of a very large number of scientific investigations, concerning their chemical composition or pharmacological properties, whether in animals and humans. In addition to generating data that support the development of new medicines, such works can also guarantee the safety and effectiveness of the use of these plant species in phytotherapy programs, as magistral or officinal formulations or industrial products. Studies focusing on *Mikania* species demonstrating the relation between pharmacological activity and chemical composition are more frequent than those reporting clinical studies of herbal derivatives from the genus, which are more important to guarantee the safety of a formulation. Therefore, this work presents a systematical review of *Mikania* genus, including nonclinical and clinical studies. The review involves studies already published on pharmacology, toxicology, and kinetics of samples prepared from *Mikania* species and aims to provide a reference base that contributes to build a wide scenario of the genus, which contributes for better understanding of their characteristics and for supporting the broad range of products and services based on popular phytotherapy.

MATERIALS AND METHODS

Survey tools, data selection, and organization

Databases queried and keywords used

A systematic review was performed consisting of a search in several databases such as Medline (by PubMed), ScienceDirect, Scopus, Lilacs, Scielo, Google Scholar, and Periodicos Capes without prior selection of dates to fetch all the articles of several years available until July 2017. The search was performed using the following keywords: "*Mikania*," "toxicology," "pharmacology," "pharmacokinetic," and "clinical" always using the strategy of combining them: "*Mikania*" and "pharmacology", or "*Mikania*" and "pharmacokinetic," or "*Mikania*" and "toxicology," or "*Mikania*" and "clinical."

Article selection criteria

Only scientific articles published in journals were selected. Theses, dissertations, and conference abstracts were not considered.

Organization of collected data

This work is organized in two sections containing results of experiments performed in nonclinical investigations, comprehending *in vitro* and *in vivo* experiments, and clinical studies. Each section comprises different activities assayed and reported in the selected articles.

RESULTS AND DISCUSSION

The systematic search in several databases allowed to observe that Google Scholar offers higher number of articles using "*Mikania*" as keyword, reaching around 16,700 titles (excluding citations), and Lilacs provided the smallest list of articles, according to Figure 1. The search has found no data on patents or books.

Performing an advanced search, associating keywords, the number of articles reduced significantly, as observed in Table 1. The base Google Scholar, again, showed higher number of references in all strategies. This occurs probably because the platform encompasses other databases. The results achieved using the combination "*Mikania*" and "pharmacology" provided the largest number of articles. Searching for clinical studies, however, it can be observed that the articles, in most databases, using the keyword "clinical," do not differentiate tests by those in experimental animals or humans.

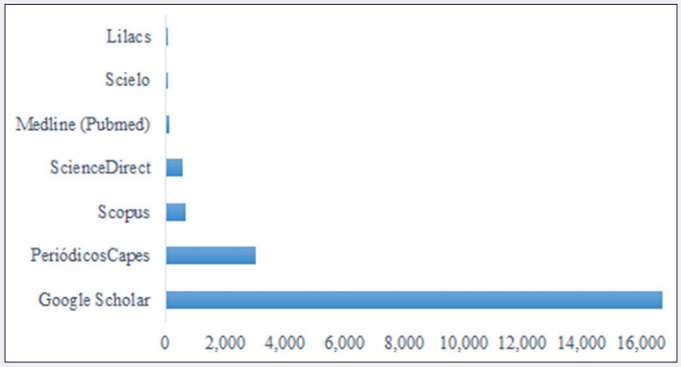

Figure 1: All results for word "*Mikania*"

Table 1: Number of articles collected, according to the used keywords

Database	Pharmacology	Pharmacokinetic	Toxicology	Clinical study
Google scholar	1680	203	1410	>1600
Periódicos Capes	188	21	110	189
Scopus	6	1	2	16
Science direct	60	23	30	92
Medline (PubMed)	79	1	1	1
Scielo	3	0	3	4
Lilacs	21	0	3	0
Total	2037	249	1559	>1902

The lowest number of articles was obtained using "*Mikania*" and "pharmacokinetic" as keywords providing 249 articles, which indicates that this topic needs to be further investigated for a better understanding of the kinetics of the substances present in the genus and thus bring up enough data to guarantee more safety for use.

Nonclinical studies

In vitro

Cytotoxicity and anticancer activities

Hexanic and ethanolic extracts from *M. laevigata* were tested for cytotoxicity against tumor and nontumor cells which presented inhibitory activity, these extracts show selectivity for both cell types.[21]

Sesquiterpene lactones isolated from *Mikania micrantha* have their anticancer activity evaluated *in vitro* on six human tumor cell lines and exhibited antiproliferative activity,[22] and the aqueous extract from the same species inhibited the activity of K562 and Hela cells *in vitro* and the growth of S180 sarcoma cells, *in vivo,* through multiple mechanisms including inhibition of proliferation, induction of apoptosis, and arrest of cell cycle, showing, additionally, low toxicity on immune system.[23]

The diterpene, *ent*-pimara-8,[14] 15-dien-19-oic acid, and three thymol derivatives, 10-acetoxy-8,9-dehydro-6-methoxythymol butyrate, 10-acetoxy-8,9-epoxy-6-methoxythymol isobutyrate, and acetylschizoginol from *Mikania decora* exhibited significant cytotoxic activity against a panel of human tumor cell lines.[24]

Anti-inflammatory activity

Anti-inflammatory activity is one of the most investigated aspects in *Mikania* genus. This activity of hydroalcoholic extracts of *Mikania scandens* roots and aerial parts was surveyed using the *in vitro* protein denaturation and the experiments indicated that the denaturation of

the protein (albumin) was inhibited in a concentration-dependent way, for both extracts, but the root extract was more active.[25] Similar results were found by Banerjee *et al*., who investigated hydroalcoholic extracts from leaves and stem. The leaf extract exhibited a more potent anti-inflammatory *in vitro* activity by denaturation of protein (egg albumin) model, higher than the stem extract.[15]

For *Mikania cordifolia*, a phenolic constituent isolated from a leaf extract – 3,5-di-O-caffeoylquinic acid – showed an *in vitro* anti-inflammatory activity expressed as inhibition of monocyte migration and superoxide anion production.[26]

Antibacterial activity

The antibacterial activity of aqueous and methanolic extracts from *M. micrantha* was tested against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris,* and *Enterobacter aeruginosa*; both the extracts were active against all microorganisms, except the latter.[27] From the same species, mikanolide and two derivatives were isolated from organic extract using chromatographic methods and were investigated for their antibacterial activity. The investigation revealed that the substances show antibacterial activity, but only pathogenic *S. aureus* and beta hemolytic *Streptococcus* Group A were susceptible at 100 µg of each substance per disc.[28]

The antibacterial activity of the isolated compounds from *M. micrantha* chloroform extract was evaluated, and all the isolated compounds (deoxymikanolide, scandenolide, dihydroscandenolide, mikanolide, dihydromikanolide, and m-methoxybenzoic acid) were effective against the tested strains. Deoxymikanolide, a sesquiterpene lactone, showed the strongest activity.[29]

Ethanolic extract and its hexane and ethyl acetate fractions of *M. laevigata* and *M. glomerata* were tested against oral pathogens. The hexane fraction from both plant extracts was the most effective in inhibiting the growth of the tested bacterial strains (minimum inhibitory concentration [MIC] values between 12.5 g/ml and 400 g/ml and minimum bactericidal concentration values between 25 and 400 g/ml, respectively), indicating that the biologically active substances have low polarity and are present mostly in the hexane fraction of both *Mikania* species, which showed remarkable inhibitory activities against *Streptococcus mutans*.[30]

The hexane extract of *M. glomerata* was tested against the multiresistant strain of *S. aureus* PI57, whereby it showed significant inhibition zone.[31] From the same species, an extract with high content in kaurenoic acid was tested *in vitro* against several cariogenic bacteria achieving to inhibit the growth of microorganisms responsible for dental caries at relatively low MIC values.[32] For the same species, the antibacterial activity against *S. aureus* of a hydromethanolic extract was evaluated, showing positive result and also a synergic effect with some antibacterial drugs already widely in use.[33]

The effect of a tincture from *M. glomerata* on *Streptococcus mutatis and Streptococcus oralis*, an oral bacterium that cause tooth losses, was evaluated which manifested bacteriostatic and bactericide effects.[34] Another article reports the potential activity of an extract rich in *ent*-kaurenoic acid obtained from *M. glomerata* against bacteria that can cause endodontic infections. It states that this extract and its major constituent *ent*-kaurenoic acid show *in vitro* antibacterial activity, the latter being a potential biofilm inhibitory agent.[35] The effect of extracts and formulations (antiseptic solutions and syrups) containing *M. glomerata*, with or without propolis, on bacterial growth was evaluated on *S. mutans* ATCC 25175 by agar diffusion method and both, extracts and formulations containing this species, were active against the bacteria.[36]

Diterpenes isolated from leaves of *Mikania hirsutissima* were evaluated for antibacterial activity on microorganisms responsible for bovine mastitis, whereby they presented satisfactory MIC (1.56–6.25 µg/ml) against *S. aureus* (ATCC and clinical isolate), *Staphylococcus epidermidis*, *Streptococcus agalactiae,* and *Streptococcus dysgalactiae*, thus this derivative can be used to control Gram-positive bacteria related to bovine mastitis.[37]

The antibacterial activity of an ethanolic extract of *Mikania cordata* was tested against *Salmonella typhi*, *Shigella sonnei*, *Proteus* spp., *Pseudomonas aeruginosa*, *Enterococci*, *Streptococcus pyogenes*, *Shigella flexneri*, *Shigella dysenteriae*, *S epidermidis,* and *S. aureus*, both Gram-positive and Gram-negative bacteria, and showed moderate results.[38]

Effect on smooth muscle

The bronchodilator activity of *M. glomerata* Sprengel derivatives (aqueous and hydroethanolic extracts and dichloromethane fraction) was tested on human bronchi and guinea-pig trachea, both presented relaxation activity and inhibited the histamine contractions, indicating that *M. glomerata* products are useful to treat respiratory diseases where bronchoconstriction is present. In the same experiment, the dichloromethane fraction showed also a light vasodilator effect on the isolated mesenteric vascular bed and on isolated rat aorta.[39] The antispasmodic effects of *M. micrantha* Kunth and *M. cordifolia* (L. F.) Willd aqueous extract were verified on isolated rat intestine, the observed antispasmodic effect could be associated to a noncompetitive Ca2+-influx.[40]

Antifungal activity

The antifungal activity of deoxymikanolide, scandenolide, dihydroscandenolide, mikanolide, dihydromikanolide, and m-methoxybenzoic acid, substances isolated from *M. micrantha* chloroform extract, was evaluated, and all the isolated compounds were effective against the tested strains, showing deoxymikanolide, a sesquiterpene lactone, with the strongest activity.[29]

The essential oil and extracts (chloroform, ethyl acetate, and methanol) of *M. scandens* were tested for antifungal activity, which was assayed using disc diffusion technique and determining MIC. The samples showed an important potential antifungal activity as mycelial growth inhibitor, against the tested phytopathogenic fungi.[41] The essential oil of *M. glomerata* exhibits anti-candida action verified by MIC test, which may be associated to the presence of terpene constituents in the oil.[42]

Antiparasitic activity

Some terpenes present antiparasitic activity, like the kaurenoic acid, isolated from an ethanolic extract from *Mikania obtusata* leaves and characterized as a trypanocidal component of the extract.[43] The diterpene *ent*-pimara-8 (14),15-dien-19-oic acid and three thymol derivatives, 10-acetoxy-8,9-dehydro-6-methoxythymol butyrate, 10-acetoxy-8,9-epoxy-6-methoxythymol isobutyrate, and acetylschizoginol, from *M. decora* exhibit *in vitro* anti-leishmanial and trypanocidal activities against *Leishmania amazonensis*, axenic amastigotes, and *Trypanosoma cruzi*, trypomastigotes,[24] and the diterpene *ent*-9*alfa*-hydroxy-15b-E-cinnamoyloxy-16-kauren-19-oic acid obtained from *Mikania stipulacea* and the sesquiterpene lactone-8*beta*-hydroxyzaluzanin-D isolated from *Mikania hoehnei* were tested on *T. cruzi* Y strain, both compounds being active.[44]

Mutagenic effect

The capacity to induce DNA damages and the mutagenic effects of the infusion from *M. glomerata* (IM) were evaluated *in vitro*, on hepatoma tissue culture cells, with comet assay and micronucleus test. The extracts tested at different doses were prepared differently as infusion and macerate in 80% ethanol from *M. glomerata*. In the comet assay, all extracts demonstrated genotoxic effects, but in the micronucleus test, except at 40 µL IM/mL culture medium, all treatments were not

mutagenic, and these effects did not show direct relation to the coumarin quantity present in infusion and macerate. The results demonstrated DNA damages at the highest concentrations of alcoholic macerate (10 and 20 μL/mL) and infusion of *M. glomerata* (20 and 40 μL/mL), therefore, both dose and preparation form shall be used with caution.[45] However, another study, using a dichloromethane fraction obtained from the hydroethanolic extract of *M. glomerata* leaves when tested on plasmid DNA, did not damage the DNA.[39]

Monoamine oxidase inhibitory activity

The inhibitory activity on monoamine oxidase (MAO) of *M. glomerata* preparations was evaluated using a mitochondrial suspension where the hexane and dichloromethane extracts were active on the MAO-B isoform, without effect on MAO-A isoform, while the methanolic extract presented inhibitory activity on both isoforms (MAO-A and MAO-B), thus showing no selectivity.[31]

Antiviral activity

The investigation of compounds isolated from *M. micrantha* revealed that some sesquiterpene lactones exhibited antiviral action against influenza virus, which brings an important perspective for new therapies against respiratory virus.[46]

In vivo studies

Antiulcer activity

The antiulcer activity of the alkaloid fraction obtained from an ethanolic extract of the leaves of *M. cordata* was evaluated using a sodium diclofenac-induced gastric ulcer model and the results of the study revealed that this fraction from *M. cordata* shows antiulcer effects.[47,48] Another preparation, a methanolic extract from root of *M. cordata* (Burm., B. L. Robinson), was investigated for a possible ulcer-protective activity on male Sprague-Dawley rats, and it was found that *M. cordata* root extract possesses antiulcer activity and that the observed activity may be due to the modulation of defensive factors through an improvement of gastric cytoprotection.[49]

The hydroethanolic extract of *M. laevigata* and coumarin obtained from it were tested aiming to evaluate their activity in gastric ulcer using different animal models, where the crude hydroalcoholic extract reduced the ulcerative lesion index induced by indomethacin, ethanol, stress, and reserpine in rats and, in the pyloric ligation model, a decrease of 53% was observed, suggesting that the pharmacological mechanism is related to an antisecretory activity that may be mediated by the parasympathetic system.[50]

Antibacterial activity

The antibacterial and cytotoxic properties of ethanolic extract from leaves of *M. cordata* were tested against four Gram-positive and six Gram-negative bacteria at different concentrations using the disc diffusion method, where the extract showed moderate antibacterial action mainly against *S. flexneri*. Comparatively, Gram-positive bacteria demonstrated more susceptibility to the extract than the Gram-negative bacteria, and the cytotoxic property of the sample was verified using Brine shrimp lethality bioassay where it did not show noticeable toxicity.[51]

Hepatoprotective effect

The hepatoprotective effect of *M. scandens* was tested in animal model using rats, in which the injury was produced by ethyl alcohol and drugs such as paracetamol and sodium diclofenac, showing that ethanolic extract and fractions have a promising hepatoprotective effect.[52,53]

The effect of a methanolic fraction of a petroleum ether extract obtained from roots of *M. cordata* (Burm., B. L. Robinson) was investigated on a possible ulcer protective activity in male Sprague-Dawley rats. The evaluation could determine its effects on Phases 1 and 2 of the hepatic drug-detoxifying enzyme system in rats. It was found to have very little or, actually, no effect on hepatic microsomal cytochrome P-450 and cytochrome b contents, as well as NADPH cytochrome C reductase activity. It caused a remarkable induction of uridine diphosphate-glucuronyltransferase (UDP-GT) activities of liver microsomes. The extract also significantly increased the activity of microsomal uridine diphosphoglucose dehydrogenase and reduced nicotinamide adenine dinucleotide phosphate: quinine reductase and cytosolic glutathione (GSH) S-transferases, with a concomitant elevation in the contents of reduced GSH. These effects were found to be dose dependent and maintained during 12-week treatment period, indicating that the intracellular contents of active intermediates of various xenobiotics including chemical carcinogens would be reduced by the specific enhancement of drug-detoxifying enzymes in the liver of rats treated with the plant extract.[49]

Effects on central nervous system

The ethanolic extract from leaves of *M. scandens* shows CNS depressant effects in mice.[18] Neuropharmacological assays using hydroethanolic extracts from aerial parts and roots of the same species showed, in experimental animal models, significant and dose-dependent central anti-nociceptive, locomotor depressant, muscle relaxant, and sedative-potentiating effects, demonstrating its depressant action on the CNS, indicating that both aerial parts and roots of *M. scandens* possess prominent depressant action on the CNS, as manifested in these neuropharmacological experiments on mice.[54,55]

The methanolic extract of *M. cordata* root possesses significant CNS depressant action and also analgesic activity.[56] Similarly, the effects of ethanol extract of leaves of *M. glomerata*, standardized, were verified on the amino acids of the hippocampus, leading to sedative and anxiolytic actions, which may be mediated by GABAergic system, and was able to increase gamma- aminobutyric acid (GABA) levels and reduce glutamate and aspartate concentrations in mouse hippocampus, which can directly and/or indirectly assist in their anxiolytic effect.[57]

Antiprotozoal activity

The antiprotozoal effect of aqueous and organic, dichloromethane/methanol (1:1), extracts from four *Mikania* species was tested against *T. cruzi* and *Leishmania braziliensis*. The organic extracts from *M. micrantha*, *M. periplocifolia*, *M. parodii,* and *M. cordifolia* showed significant *in vitro* antiprotozoal activity against *T. cruzi*, epimastigotes, and *L. braziliensis*, promastigotes. The *M. micrantha* organic extract was the most active against the two protozoans. All aqueous extracts showed moderate-to-low activity against *T. cruzi* and *L. braziliensis*.[58]

Anti-ophidian activity

In 2005, Maiorano *et al*.[59] evaluated aqueous extracts prepared from fresh dried roots, stems, and leaves of *M. glomerata,* where the extracts efficiently neutralized different toxic, pharmacological, and enzymatic effects induced by *Bothrops* and *Crotalus* snake venoms. Phospholipase A2 activity and the edema induced by *Crotalus durissus terrificus* venom were also inhibited. The hemorrhagic activity of *Bothrops* venoms and the clotting activity of *C. durissus terrificus*, *Bothrops jararacussu,* and *Bothrops neuwiedi* venoms were totally inhibited.[59] In addition, the dichloromethane fraction of the hydroalcoholic extract from the same species had a significant reduction of the edema induced by subplantar injections of *Bothrops jararaca* venom in mice.[39]

In another study, the hydroethanolic leaf extract from *M. glomerata* showed significant activity on Wistar rats treated with *B. jararaca* snake venom depicted as a significant reduction of the inflammation cells migration, a marked decrease in edema and also a significant reduction in the intensity of the hemorrhagic effects.[60]

For the same species, *M. glomerata*, the levels of pro-inflammatory and anti-inflammatory cytokines were evaluated, as well as the effect of the conventional treatment against snakebite in comparison to the effect of this treatment was complemented with extract from *M. glomerata* in experimental intoxication by *Bothropoides jararaca*. The results showed that botulinum toxin poisoning mainly stimulated the production of serum interleukin (IL)-6 and tumor necrosis factor-alpha, IL-1β, and IL-6 in the paw homogenate of experimentally intoxicated animals. The complementary treatment with the extract from *M. glomerata* had a major influence on the production of IL-6, IL-10, and IFN-γ in the serum and IL-6, IL-1β, and IFN-γ in the homogenate.[61]

Antidiarrheal activity

The investigation of the antidiarrheal activity of the aqueous extract from leaves of *M. glomerata* 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. These findings suggest that the aqueous extract of the leaves of *M. glomerata* might elicit an antidiarrheal effect by inhibiting intestinal motility.[62]

The antidiarrheal activity of the ethanolic extract of the leaves of *M. cordata* was evaluated in mice and it significantly reduced the number of bowel movements, when compared to a control group.[63]

Cytotoxicity and genotoxic activities

The n-butanolic extract of *M. micrantha*-containing flavonoids was selected for anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell line cell line in Swiss albino mice where the extract expressed dose-dependent anticancer activity attributed to the presence of polyphenolic groups.[64] Moreover, the potential biological activity of the hydroethanolic extract of *M. laevigata* on the genotoxicity induced by alkylating agents (methyl methanesulfonate and cyclophosphamide), using the comet assay, was verified, and the results showed that the treatment with *M. laevigata* extract, previously compared to methyl methanesulfonate and cyclophosphamide administration, reduced DNA damage in mice.[65]

Antinociceptive and anti-inflammatory activities

Ethanolic extract from dried leaves of *M. cordata* was tested for its possible antinociceptive, cytotoxic, and antibacterial activities in animal models, where the extract produced significant writhing inhibition in acetic acid model in mice at the oral doses of 125 and 250 mg/kg body weight ($P < 0.001$), comparable to the standard drug, sodium diclofenac, at the dose of 25 mg/kg of body weight. The crude extract produced moderate cytotoxic activity against brine shrimp *Artemia salina* ($LC_{50} = 90$ and $LC_{90} = 166$ μg/ml).[38]

The crude extract of *M. cordata* (crude petrol: Et_2O:MeOH 1:1:1) and an isolated sesquiterpene, deoxymikanolide, significantly inhibited acetic acid-induced writhing in mice, suggesting an antinociceptive activity of *M. cordata* extract.[66]

The aqueous extract of *Mikania lindleyana* exhibited anti-inflammatory and antinociceptive activities in different animal models.[67] In addition, the methanolic extract of *M. lindleyana* presented anti-inflammatory and antinociceptive activities that may be related to opioid mechanism.[68]

Carrageenan-induced inflammation was significantly antagonized by *M. scandens* hydroethanolic leaf extract, showing 50% inhibition at a dose of 1000 mg/kg.[15] The study of the antinociceptive activity of a hydroethanolic extract from flowers of *M. scandens* showed significant dose-dependent anti-nociceptive, locomotion skeletal muscle relaxation, and sedative-potentiating effects ($P < 0.001$), demonstrating its depressant action on the murine CNS. It allows to conclude that the flower of *M. scandens* possesses a prominent antinociceptive property along with marked hasty action on the CNS of mice.[16]

Analgesic activity of methanolic extract of *M. scandens* was investigated using the tail flick technique in mice, where it presented a distinct analgesic property.[69]

The anti-inflammatory activity of the sesquiterpene lactones from *M. micrantha* was tested in ear model of edema induced by Acetate 12-*O*-tetradecanoylphorbol (TPA), where they exhibited moderate activity.[22]

Ethanolic extract from leaves of *M. micrantha* was used to evaluate the central and peripheral antinociceptive activity where it was observed that this extract produced significant analgesic activity, both centrally and peripherally; in addition, the acute oral toxicity test showed no sign of toxicity or mortality.[70]

The hydroethanolic extract and isolated substances (coumarin and *o*-coumaric acid) of *M. laevigata* leaves were tested in a model of allergic pneumonitis using mice, where it was possible to observe reduction, after the treatment period, of the influx of inflammatory cells into the site of the lesion when compared to the control, mainly eosinophils, which demonstrates an important activity of the extract, and its constituents, in allergic inflammation.[11] Dichloromethane fractions (MG) obtained from the ethanolic extract of *M. glomerata* were evaluated for possible antiallergenic effect and anti-inflammatory activity on models of ovalbumin-induced allergic pleurisy and in models of local inflammation induced by biogenic amines, carrageenan, and platelet-activating factor (PAF). Plasma exudation as well as neutrophil and eosinophil infiltration evoked by the pleural injection of the antigen was significantly reduced by the fraction. Likewise, PAF-induced pleural neutrophil migration was inhibited by the treatment with a dichloromethane fraction, but pretreatment of the animals with dichloromethane fraction failed to modify the pleurisy induced by histamine, serotonin, or carrageenan. This suggests that MG1 is effective in inhibiting immunologic inflammation but does not affect acute inflammatory response caused by other agents.[10]

By evaluating the effect of pretreatment with extracts of *M. glomerata* and *M. laevigata* in inflammation and oxidative stress in the lungs of rats exposed only to intratracheal inhalation of coal dust, it was observed that after 15 days of treatment, a reduction in cell count can be observed, suggesting that both extracts play a role in the prevention of oxidative injuries in lung, caused by exposure to coal dust.[12]

The anti-inflammatory activity of the hydroethanolic extract of *M. laevigata* was assayed by interference in vascular permeability and leukocyte function in peritonitis induced by carrageenan in mice. The extract decreases the vascular permeability and also the leukocyte rolling and adhesion into the inflamed tissues by a mechanism dependent on nitric oxide; this may occur by inhibition of pro-inflammatory cytokine production at the inflammatory site.[14]

Anti-inflammatory activity

Anti-inflammatory potential of leaf and stem decoctions of *M. laevigata* and *Mikania involucrata* was evaluated using paw edema and pleurisy models induced by carrageenan, in which the decoctions of the leaves of both species were more effective than those of stems in reducing the inflammatory compound in the model of paw edema. Moreover, by the pleurisy assay, decoctions of *M. laevigata* and *M. involucrata* leaves inhibited the migration of leukocytes to the pleural exudate.[13]

Toxicity

The *in vivo* toxicity evaluation of *M. glomerata*-standardized ethanolic extract was performed in mice that received oral severe doses of the extract for 30 consecutive days, leading to estimate LD_{50} at around 3000 mg/kg. A macroscopic morphological analysis of the main organs and the acute toxicity evaluation, performed using mouse biochemical

and hematological parameters, allowed to classify the extract as nonnoxious, as it did not produce any morphological alterations in the main organs and in the biochemical and hematological parameters of the mice.[71]

A study that aimed to analyze the toxic effects of dried aqueous extract from *M. glomerata* during the gestational period of hypertensive rats allowed to observe that the extract from this species did not show the possibility of teratogenicity; it also showed no influence on vasoconstriction of hypertensive rats at the tested concentrations. The histological analysis leads to conclude that no significant alterations among the analyzed groups can be observed.[72]

The hydroalcoholic extract from *M. glomerata* produced no genotoxic damage in mice, but significantly increased the frequency of micronucleated polychromatic erythrocytes (MNPCEs) induced by doxorubicin, indicating a drug–drug interaction (potentiating the doxorubicin-induced mutagenicity). This rise was not accompanied by lipid peroxidation or antioxidant level reduction, as measured by malondialdehyde and the antioxidants GSH and Vitamin E. Despite the presence of coumarin (a known antioxidant), hydroalcoholic extract may exert adverse effects probably in association with mutagenic compounds, although this effect on DNA damage did not involve oxidative stress,[73] but in the analysis of the genotoxicity and cytotoxicity of the extract rich in kaurenoic acid from *M. glomerata* using the assay of frequency of MNPCEs and PCE/normochromatic erythrocytes ratio, it was not possible to observe any genotoxic or cytotoxic changes in mice.[32]

In the spermatogenic cycle of adult male rats, the hydroethanolic extract of *M. glomerata* did not significantly alter body and organ weights nor did interfere on gamete production, serum testosterone level, or food intake.[74] Moreover, the administration of hydroethanolic extract of *M. glomerata* did not show any impairment of fertility and no significant difference in the analyzed parameters, suggesting an absence of mutagenic effect on male Wistar rats.[75] The effect of the hydroalcoholic extract, prepared from aerial parts of *M. glomerata*, was also evaluated regarding the reproductive system of rats submitted to chronic treatment, in which no significant alteration of the analyzed variables was observed and the treatment did not affect the food consumption. These data suggest that the hydroalcoholic extract of *M. glomerata* shows no toxic effect and do not interfere on the fertility of Wistar rats, undergoing long-term treatment.[76]

Acute toxicity of the aqueous, petroleum ether, methanol, and chloroform extracts from *M. scandens* was evaluated by oral administration to different groups of mice at the doses of 1000, 2000, and 3000 mg/kg body weight. After administration of the extracts, animals were observed continuously for the first 3 h and continued at regular intervals for 24 h in order to detect any alteration in their behavior, but none was killed by the dose. Hence, it is proven that the drug has very low toxicity, at these doses.[69]

In the acute toxicity study of the extract from leaves of *M. cordata* where only female mice were treated with 5, 50, 300, and 2000 mg extract/kg body weight, respectively, the mice were monitored for 24 h after administration to determine any behavioral, neurological, and autonomic occurrence and, after 14 days, to verify mortality. During the observation period, neither behavioral change symptoms nor any mortality was recorded, so the extracts were considered safe.[63]

The n-butanolic extract from *M. micrantha* containing flavonoids was tested for anticancer activity against EAC cell line in Swiss albino mice and also to check the acute toxicity, where the extract's dose-dependent anticancer activity could be attributed to the presence of polyphenolic groups. Furthermore, the extract did not show any toxic reactions and mortality up to a dose of 2000 mg/kg.[64]

Clinical studies

Among few clinical studies about *Mikania* species, most of them report studies performed using syrups and mainly ointments containing derivatives of this species. One of these shows the clinical safety in using an herbal formulation combining *M. glomerata* and other species to treat respiratory diseases used in 26 healthy adult volunteers of both sexes during 28 uninterrupted days where, after the necessary analysis, no toxicity was observed.[77]

In addition, the clinical safety of a syrup containing "guaco" tincture *(M. glomerata)*, in association with other species (*Grindelia robusta, Copaifera officinalis, Myroxylon toluifera, and Nasturtium officinale)*, the main indication of which is to treat respiratory affections, was evaluated and it was well tolerated in an uncontrolled clinical trial on 24 volunteers of both sexes, who received 15 mL of the syrup, four times daily for 21 uninterrupted days without serious adverse events.[78]

A study performed to evaluate the safety and the genotoxic potential of "Melagrião," an herbal medicine composed by six plant extracts among them, *M. glomerata*, was carried out on adult volunteers for 28 days, evaluating the clinical toxicology and genotoxicity, as result no evidences of toxicity were detected.[79]

Regarding the kinetic profile of the main metabolites of guaco syrup, the evaluation was performed in healthy humans who received 60 mL of syrup containing 1500 mg of coumarin. After administration, the kinetic profile in the blood was evaluated and the result showed that o-coumaric acid is one of the main bioavailable metabolites of coumarin and not 7-hydroxycoumarin; therefore, the hydrolysis of the lactone ring forming a carboxylated compound is one of the possible metabolic routes for coumarin in humans.[80]

A study conducted to determine the safety and efficacy of an ointment containing methanolic extract of *M. cordata* showed the safety of the formulation and that it is pharmacologically comparable to mupirocin and therefore could be used for the treatment of superficial lesions.[81]

CONCLUSION

Genus *Mikania* is distributed throughout Brazil predominating in the southern and southeastern regions. It comprises species of

Table 2: *In vitro* and *in vivo* studies with *Mikania* genus

Studies	Articles
In vitro	
Cytotoxicity and anticancer	4
Anti-inflammatory	3
Antibacterial	11
Bronchodilator, antispasmodic, and vasodilator	3
Antifungal	3
Antiparasitic	3
Mutagenic	2
Monoamine oxidase inhibitors (MAOIs)	1
Antiviral	1
In vivo	
Antiulcerogenic	4
Antibacterial	1
Hepatoprotective	4
CNS	6
Antiprotozoal	1
Anti-ophidian	4
Antidiarrheal	2
Cytotoxicity	2
Antinociceptive	7
Anti-inflammatory	9
Toxicity	10

CNS=Central nervous system

pharmaceutical and phytochemical interests too. This systematic review shows that there are many popular alleged uses and a substantial number of articles dealing with different pharmacological activities for different species of the genus, either *in vitro* or *in vivo* [Table 2]. However, the number of clinical and pharmacokinetic studies reported is still low, even though *M. glomerata* and *M. laevigata* are already inserted in the formulary of phytomedicines of the Brazilian Pharmacopoeia.

The most studied species so far are *M. glomerata, M. laevigata, M. scandens,* and *M. micrantha*, the first two being widely used in Brazil to treat respiratory disorders and are present in various pharmaceutical formulations in the local retail market.

Among the pharmacological activities, anti-inflammatory, analgesic, antibacterial, and CNS were the most referred, which are directly related to the alleged popular use of this genus species. In addition, a great number of toxicological tests on animals have also been carried out. This systematic review intends to gather the pharmacological knowledge published about *Mikania* species and thus contribute to give scientific base for a safe use of derivatives from the species here cited.

Acknowledgments

We would like to thank CAPEs for the scholarship granted and the UFPA for the facilities.

Financial support and sponsorship

ASBS thanks CAPES - Coordination for the Improvement of the Academic Personnel for the grant received during her doctorate.

Conflicts of interest

There are no conflicts of interest.

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