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Review

Scientific evidence for *Mikania laevigata* and *Mikania glomerata* as a pharmacological tool

Marcelo H. Napimoga[a] and Regiane Yatsuda[b]

[a]Laboratory of Biopathology and Molecular Biology, University of Uberaba and [b]Laboratory of Physiology and Pharmacology, Federal University of Bahia, Brazil

Abstract

Objectives Historically, the majority of new drugs have been generated from natural products as well as from compounds derived from natural products. In this context, *Mikania laevigata* and *M. glomerata*, popularly known as 'guaco', have a long history of use. Brazilian Indians have an ancient tradition of using 'guaco' for snakebites. In current herbal medicine in Brazil, 'guaco' is used as an effective natural bronchodilator, expectorant and cough suppressant employed for all types of upper respiratory problems including bronchitis, pleurisy, colds and flu, coughs and asthma.

Key findings In Brazil, this plant has been widely used, even as commercial preparations. Its medicinal properties are widely recognized, mainly in the treatment of inflammatory conditions, bronchodilator activity, anti-ulcerogenic, antiophidian as well as antibacterial and antiparasitic activity, although the efficacy of the antibacterial activity is so far controversial.

Summary The studies on *Mikania glomerata* and *M. laevigata* have provided scientific evidence that those plants have a considerable anti-inflammatory therapeutic potential.

Keywords inflammation; medicinal plant; *Mikania glomerata*; *Mikania laevigata*; phytotherapy

Introduction

The use of medicinal plants in the world, and especially in South America, contributes significantly to primary health care and knowledge on medicinal plants. Sometimes it is the only therapeutic resource of some communities and ethnic groups.[1] In a constant attempt to improve their quality of life, humans have used plants as sources of food, shelter, clothing, medicine, cosmetics, and for seeking relief from the hardship of life. Some plants are known as medicinal because they contain active substances that cause certain reactions, and bioactive molecules with a considerable therapeutic potential.

The history of drug development has its foundation firmly set in the study of natural medicine used to treat human diseases over the centuries. Analysis of medicinal plants, bioactive cultures, and increased understanding of micronutrients in the food chain opened the field to the development of purified and defined chemical compounds as dose-controlled medicines. Efforts to subject botanicals to rigorous scientific research began recently; however, there are still many problems associated with this area of research. These include procuring the study agents, selecting the appropriate study method and clinical trial design, navigating through regulatory obstacles, and obtaining funding. Evidence-based botanical research can help to validate traditional uses and to facilitate new drug development.[2]

Natural products have been the most productive source of leads for the development of drugs. Over one hundred new products are in clinical development, particularly as anticancer agents and anti-infectives.[3] Nowadays the application of molecular biological techniques is increasing the accessibility of new compounds that can be suitably produced in bacteria or yeasts, and combinatorial chemistry approaches are being based on natural product scaffolds to create screening libraries that closely resemble drug-like compounds. To confirm that natural products are the major source of new compounds which will be used by the pharmaceutical industry, Newman and Cragg[4] demonstrated that, overall, of the 1184 new chemical entities covering all diseases/countries/sources between 01/1981 and 06/2006 only 30% were synthetic in origin, thus demonstrating the influence of 'other than formal

Correspondence: Marcelo H. Napimoga, Laboratory of Biopathology and Molecular Biology, University of Uberaba, Av. Nenê Sabino, 1801, Uberaba, Minas Gerais 38055-500, Brazil. E-mail: marcelo.napimoga@uniube.br

synthetics' on drug discovery and approval. In this context, the *Mikania* genus is an important source and a promissory plant to be used in different diseases. In this review, we have focussed on some scientific studies of *Mikania laevigata* and *M. glomerata* to provide the evidence for the diversity of medical applications provided by these plants.

Mikania species

Plants of the genus *Mikania* were described by Willdenow in 1804, receiving this nomenclature in honour of Professor Joseph Gottfried Mikan, Prague. The genus *Mikania* Willd is the largest genus of the tribe Eupatorieae (Asteraceae family), including approximately 450 species. Many of these species are found in South American countries, with its two major diversity centres in the highlands of south-eastern Brazil and the eastern foothills of the Andes from Bolivia to Colombia, as well as tropical regions of Asia and Africa.[5–7] The genus is widely distributed in Brazil with approximately 171 described species, with approximately 150 of these being endemic, including *M. laevigata*.[6–9]

Mikania grows as a timbered shrub with a branched cylindrical stem.[10] This plant is a sub-scrub creeper of woody branches and brilliant-green leaves that release a strong aroma reminiscent of vanilla.[11] The species are characterized by their capitula which are composed of four florets and involucres composed of four phyllaries that are subtended by a subinvolucral bract. There is no variation from this basic organization, and specific differences mostly involve the type of capitulescence, size of habit, shape of organs and plant texture.

Several species of the *Mikania* genus (Figure 1; growth habit: creeper) are popularly known as 'guaco', for example, *M. cordifolia*, *M. laevigata* Schultz Bip. ex Baker, *M. glomerata* Spreng, *M. scandens* Willd., *M. officinalis* Mart. and *M. opifera* DC.[8,12–16] *M. laevigata* Schultz Bip. ex Baker is popularly known as 'guaco', 'guaco of the home' and 'guaco of the bush', and it is a native species of southern Brazil. *M. glomerata* Spreng is popularly known as 'guaco', 'smooth guaco', 'smelling guaco', 'caatinga-vine', 'heart of Jesus', 'putty-vine' and 'snake-herb', and it is also a native species found in Mata Atlântica in south-eastern Brazil.[17,18]

Figure 1 *Mikania glomerata*

M. glomerata Spreng was considered an official species in the first edition of the *Brazilian Official Pharmacopoeia*, while *M. laevigata* was described in the sixth volume in the fourth edition of the *Brazilian Official Pharmacopoeia*.[19–21] Coumarin (1,2-benzopyrone) is the main chemical marker described for both species.[22] *M. glomerata* Spreng was identified by Sprengel in 1826, and is also known as *Cacalia trilobata* Vell., *M. amara*, *M. aspera*, *M. attenuata*, *M. scandoria* DC., *M. hederaefolia* DC., *Willoughbya glomerata* (Spreng), *Willoughbya moronoa* (Ktze). In southern Brazil, *M. laevigata* is mostly harvested, rather than *M. glomerata*, due to its local abundance.

M. laevigata and *M. glomerata* are very similar morphologically. The main difference between them is their flowering period: September for *M. laevigata* and January for *M. glomerata*. The leaves are slightly different, the lobes being more prominent in *M. glomerata*, and both present the characteristic odour of coumarin.[23] Their habitats are the shores and inland forests, adapting very well to domestic cultivation. At the time of flowering it becomes a very popular plant for honey bees.[24]

History and popular use

Many plants are used in Brazil in the form of crude extracts, infusions or plasters to treat common infections without any scientific evidence of efficacy.[1]

M. laevigata Schultz Bip. ex Baker and *M. glomerata* Spreng are the two medicinal plants in Brazil that are used interchangeably and often at times with no distinction between the two species.[1,25] The leaves of both species are used in Brazilian folk medicine and other southern American countries for several inflammatory and allergic conditions, particularly of the respiratory system.[26]

Both have a long history of use by rainforest inhabitants. Brazilian Indians have an ancient tradition of using guaco for snake bites; preparing a tea with the leaves and taking it orally as well as applying the leaves or the stem juice (in a hurry) directly onto the snake bite. Other Amazonian rainforest Indian tribes have employed the crushed leaf stem topically on snake bites (as well as drinking the decoction of leaves and/or stem) and have used a leaf infusion for fevers, stomach discomfort and rheumatism. Indigenous people in the Amazon region in Guyana warm the leaves to put on skin eruptions and itchy skin. Several Indian tribes also believe if you crush the fresh aromatic leaves and leave them around sleeping areas the spicy scent will drive snakes away. For this reason and because of its long history as a snakebite remedy, it earned the name 'snake-vine' and 'snake-herb' in herbal medicine systems.

The leaves of *M. laevigata* have been widely used as infusions or plasters, while the crude extract of this species is commonly commercialized as a phytomedicine, mainly to treat inflammatory disorders, such as bronchitis, chronic lung diseases and bronchial asthma.[24,27] In current herbal medicine systems in Brazil, 'guaco' is well known and well regarded as an effective natural bronchodilator, expectorant and cough suppressant employed for all types of upper respiratory problems, including bronchitis, pleurisy, colds and flu, coughs and asthma, as well as for sore throats, laryngitis and fever. The *M. glomerata* and *M. laevigata* plants have been widely used based on their folk indications in asthma and bronchitis, probably due to their anti-allergic, bronchodilating, anti-inflammatory and anti-oedematogenic properties.[28–32]

In 1870, a Brazilian herbal drug called *Opodeldo de Guaco* was made from the leaf and stem of 'guaco' that was considered a 'saint's remedy' to treat bronchitis, coughs and rheumatism. This 'drug' is still a popular home remedy today throughout Brazil for the same purposes, but locals prepare it themselves by boiling 'guaco' leaves into a tasty spicy cough syrup. Nowadays, this plant and its syrup are commercialized and distributed for free by Brazilian government health programmes to treat respiratory complaints such as asthma, bronchitis and cough. Although this clinical conduct has been described as harmless and safe, neither the assessment of the toxicity of 'guaco' syrup used by humans, nor its efficacy or mechanisms of action have been investigated properly.[33]

Guaco is also popular in Brazil as an anti-inflammatory, antispasmodic and pain-reliever for rheumatism, arthritis, intestinal inflammation and ulcers. A decoction of the leaves is employed externally for neuralgia, rheumatic pain, eczema, pruritus and wounds. Ethnopharmacological studies of the *Mikania* genus showed pharmacological properties such as tonic, depurative, antipyretic and appetite stimulant, and as a treatment for influenza.[34,35]

Phytochemical analysis of *M. glomerata* and *M. laevigata*

Analytical methods

Studies were conducted to evaluate the best preparation methods for extracts of *M. laevigata* and *M. glomerata*. Celeghini *et al*.[11] evaluated the sample preparation method, comparing maceration and maceration under sonication. The authors obtained statistically similar results; however, as the extraction time of seven days by maceration is very long for routine analysis, maceration under sonication was chosen as the best method considering the time/yield ratio, since it required a shorter extraction time (20 min). Through visual evaluation and analysis using thin layer chromatography (TLC), the best proportion of the extracting solvent was established as being ethanol : water (1 : 1 v/v). For the two methods tested, the extraction and two sequential re-extraction tests, in the first extraction the percentage of coumarin obtained was approximately 78.73%, being reproducible and not justifying the implementation of serial extractions. From the extraction and kinetics (yield of extraction as a time function), the optimal extraction time was determined using the mixture ethanol : water (1 : 1 v/v) as the extracting solvent, and the inflection point of the curve was found at 20 min, which was chosen as the optimal extraction time.

Although the usage of *M. glomerata* and *M. laevigata* in folk medicine is widespread around the world, for the safe utilization of any plant as a medicine, its standardization is necessary to guarantee plant drug authenticity and its content of active principles according to the parameters utilized as quality criteria. The results presented by these authors indicated that high performance liquid chromatography–ultraviolet analysis (HPLC-UV) may be a useful tool for the quality control of hydroalcoholic extracts of *M. glomerata*, since this method showed reproducibility and sensitivity adequate for these extracts. There were other advantages also, such as high efficiency, speed and the possibility of its utilization in automated systems.[11]

A comparative study of the chemical composition of the species *M. glomerata* and *M. laevigata* showed that adulterations of plant raw materials often occur in the marketing of herbal medicine, usually in the form of substitutions and/or fakes. This may occur due to the difficulties of obtaining the authentic plant material, or by an intentional use of a plant species that has less economic value but shows similar morphological features.

Despite *M. glomerata* and *M. laevigata* being commercialized with no distinction in Brazil, they have been scarcely studied chemically; however several compounds have been isolated already, chiefly coumarins, diterpenes and essential oils.[11,17,23,31,36–48] Phytochemical studies of the leaves from *M. laevigata* and *M. glomerata* species indicated a similar composition, presenting coumarins, diterpene acids (entkaurene derivatives), triterpenes and steroids (friedelin, stigmasterol and lupeol), flavonic heterosides, sesquiterpene lactones and cinnamic acid derivatives.[11,14,17,23,31,36–49] However, Oliveira *et al*.[17] did not find the presence of heteroside flavones in either species. Bolina *et al*.[41] did not detect the presence of genin or heteroside anthraquinones, saponins, genin flavones, alkaloids, cardiotonic heterosides, tannins and simple phenols in either species. However, the study conducted by Oliveira *et al*.[17] reported the presence of alkaloids, saponins, tannins and polyphenols in the aerial parts of *M. glomerata* and *M. laevigata*.

The coumarin concentration has been determined in many studies, as this substance is a known marker used as a reference.[31] In a phytochemical screening for coumarin detection, the authors observed in the chromatographic profile two different species, o-coumaric acid and coumarin, of which 0.30% ± 0.01 (w/w) of coumarin was obtained for *M. glomerata* and 0.43% ± 0.02 (w/w) for *M. laevigata*.[41] These values were in accordance with the contents (minimal of 0.1%, w/w) described by the monograph of 'guaco' in the Brazilian Pharmacopoeia. The authors concluded that the results indicated similar chemical profiles for *M. glomerata* and *M. laevigata*, as well as comparable coumarin content, thus suggesting that both species may be used with no distinction between them. dos Santos *et al*.[23] determined the contents of coumarin and o-coumaric acid in hydroalcoholic and aqueous extracts (lyophilized and freshly prepared), in leaves of both 'guaco' species. They found that the

concentration for the selected markers was larger for *M. glomerata* than *M. laevigata*, not only for the aqueous fresh extract but also for the hydroalcoholic extract of *M. laevigata*, that presented considerable variations in concentration in terms of geographical origin, when collected during the same season and period and processed in the same way. The lyophilized extract presented some alteration during the lyophilization process, confirmed by a new peak detected in the corresponding chromatograms and a diminished quantity of the selected markers (60% for o-coumaric acid and 50% for coumarin) in relation to the freshly analysed aqueous extract.

In another study, the major compounds of the hydroalcoholic extract of *M. laevigata* identified were coumarin (36.90%) and dihydrocoumarin (32.30%), a lower quantity than shown by dos Santos *et al*.[23,31] The weight of dry crude extract and coumarin concentration from *M. laevigata* were determined in each month and no statistical difference was detected, and did not substantially alter the basic pharmacological activity of guaco extract.[31] Yatsuda *et al*.[39] analysed the relative percentage of the identified compounds by gas chromatography (GC–MS) of the ethanolic extract of both species of *Mikania*. They found 17.81% of coumarin in *M. laevigata* but did not detect coumarin in the ethanolic extract of *M. glomerata*, only in the ethyl acetate fraction of *M. glomerata*, at a relatively low percentage (1.43%).

Thus, the percentage of compounds in both species shows a great variation, as does the quality of compounds, depending on the geographical origin of the plants. Table 1[50] shows the chemical constituents identified in the fractions of *M. glomerata* and *M. laevigata* collected from different geographical origins.

Biological activity of fractions and constituents identified from *M. laevigata* and *M. glomerata*

Initial screenings of plants for possible antimicrobial activity typically begin by using crude aqueous or alcoholic extractions and can be followed by various organic extraction methods. Since nearly all of the identified components from plants active against microorganisms are aromatic or saturated organic compounds, they are most often obtained through initial ethanol or methanol extraction.

Pretreatment of rats with a dichloromethane fraction of *M. glomerata* was able to reduced pleural oedema, showing anti-allergic activity at the highest dose tested.[51] The administration of a dichloromethane fraction dose-dependently inhibited leucocyte infiltration detected after antigen challenge. Experiments have demonstrated an anti-allergenic effect of a dichloromethane fraction obtained from the hydroalcoholic extract of *M. glomerata* leaves in rats.[28] The

Table 1 Chemical constituents identified in fractions of *Mikania laevigata* and *Mikania glomerata*

Reference	Fractions	Constituents
Veneziani *et al*.[36]	The hexane soluble fraction of branches of *M. glomerata*	*Ent*-kaur-16(17)-en-19-oic acid and *ent*-beyer-15(16)-en-19-oic acid, en-15β-benzoyloxkaur-16(17)-en-19-oic acid
Veneziani *et al*.[36]	The CH_2Cl_2 soluble fraction of branches of *M. glomerata*	Grandifloric acid, hydroxyl-*ent*-kaur-15(16)-en-19-oic acid
Veneziani *et al*.[36]	The hexane soluble fraction of leaves of *M. glomerata*	Stigmasterol, β-sitosterol and *ent*-15-β-isobutyryloxykaur-16(17)-en-19-oic acid
Veneziani *et al*.[36]	The CH_2Cl_2 soluble fraction of leaves of *M. glomerata*	Coumarin and ortho-hydroxycinnamic acid
Ferreira *et al*.[50]	The hexane fraction of leaves of *M. laevigata*	Lupeol acetate, lupeol, kaurenoic acid, beierenoic acid, coumarin, diidrocoumarin, caryophyllene oxide and spathulenol
Ferreira *et al*.[50]	Dicholoromethane fraction of leaves of *M. laevigata*	Coumarin syringaldehyde and ortho-((50′-hydroxy)-cis-cinnamoyl)-trans-cinnamic acid
Ferreira *et al*.[50]	Ethyl acetate fraction of leaves of *M. laevigata*	*Ent*-3α-O-β-D-glucopyranoside, 16α, 17-diidroxicauran 2β-((3-O-(3-hydroxy-1-oxo-3-phenylropyl)-2-(3-methyl-1-butyryloxy)-4-O-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl)oxy)-13-15α-dihydroxy-19-norcaur-16-en-18-oic acid), trans-melilotoside, cis-melilotoside, adenosine, 3-O-β-D-glucosyl-patuletine, 3-O-β-D-glycosyl-kaempferol, 3-O-β-D-glucosyl-quercetin and 3,3′,5-trihydroxy-4′,6,7-trimethoxiflavone
Yatsuda *et al*.[39]	The hexane fractions of leaves of *M. laevigata*	Dihydrocoumarin, coumarin, spathulenol, hexadecanoic acid, 9, 12-octadecadienoic acid, 9,12,15-octadecatrineoic acid, cupressenic acid, kaurenol, kaurenoic acid, isopropyloxi-grandifloric acid, isobutyloxy-grandifloric acid
Yatsuda *et al*.[39]	The hexane fractions of leaves of *M. glomerata*	Spathulenol, caryophyllene oxide, hexadecanoic acid, 10, 13-octadecadienoic acid, 9,12-octadecadienoic acid, kaurenoic acid, diterpenic acid, grandifloric acid, isopropyloxy-grandifloric acid, diterpenic ester
Yatsuda *et al*.[39]	The ethyl acetate fractions of leaves of *M. laevigata*	Hexadecanoic acid, 9,12-octadecadienoic acid, 9,12, 15-octadecatrienoic acid, cupressenic acid, kaurenoic acid
Yatsuda *et al*.[39]	The ethyl acetate fractions of leaves of *M. glomerata*	Trans-cariofileno, coumarin, EPI-bicyclosesquiphellandrene, spathulenol, hexadecanoic acid, 8,11-octadecadienoic acid, 9,12,15-octadecatrienoic acid, kaurenoic acid, diterpenic acid

effects on isolated respiratory and vascular smooth muscle have been investigated, testing the aqueous hydroalcoholic extract, and a dichloromethane fraction obtained from the hydroalcoholic extract of *M. glomerata* leaves.

Aqueous extracts and hydroalcoholic extract induced a significant inhibition of histamine-induced contractions in the guinea-pig isolated trachea, but the active dichloromethane soluble fraction was more active than the hydroalcoholic extract.[29] Chromatographic studies performed with the dichloromethane fraction confirmed the findings of Lucas[24] and Oliveira *et al*.,[17] showing the presence of coumarin in leaves of *M. glomerata*. The concentration of coumarin in the dichloromethane fraction was very high (11.4% w/w), and coumarin probably had a very important role in the relaxant effect of *M. glomerata* on respiratory smooth muscle. Experiments performed by Soares de Moura *et al*.[29] showed that coumarin had a significant inhibitory effect on guinea-pig isolated tracheal rings precontracted with histamine, acetylcholine or K^+. Therefore, it was likely that other active participants contributed towards the bronchodilator activity of *M. glomerata* fraction (MG1). The vasodilator effect (potency) was lower than the bronchodilator effect of MG1. This suggested that the compounds present in the extracts of *M. glomerata* were more active on the respiratory smooth muscle than on vascular smooth muscle. In that study, the authors demonstrated an inhibitory effect of the dichloromethane fraction on the mouse hind-paw oedema induced by release of inflammatory agents by *Bothrops jararaca* venom, confirming an anti-infammatory action of *M. glomerata* as demonstrated by Ruppelt *et al*.[52,53]

Duarte *et al*.[54] showed that the essential oil of *M. glomerata* exerted a strong anti-*Candida* activity. The essential oil was also subjected to GC and GC–MS analyses. Among the identified compounds, some had been reported previously to have antimicrobial activity, including DL-limonene and germacrene-D, and menthol.[55–57] Yatsuda *et al*.[39] showed that the hexane fraction (with kaurenoic acid as a major compound) from both species of *Mikania* was the most effective against crude extract and ethyl acetate fractions in inhibiting growth and cell adherence to a glass surface of mutans streptococci. Another study detected that the ethanolic and dicloromethane extracts did not present antibacterial activity, and were detected only in the hexanic extract of *M. glomerata* substances with antibacterial activity.[58] The results obtained in both studies suggested that the biologically active compounds were present mostly in the hexane fraction of both *Mikania* species.

During the flowering period there is an increased concentration of compounds in the plants; for the 'guaco' plants this period is from August to December. Although these plant has been widely used, even as commercial preparations, there have been few studies on their biological properties. Some of these compounds have shown good results in comparison with positive controls in bioassays, as described in Table 2.[59–64]

The coumarins are the main biological markers found in *M. laevigata* and *M. glomerata* and were identified in various plants. The activities of coumarins are described as anti-inflammatory, expectorant, anti-ulcerogenic, anticoagulant, respiratory smooth muscle relaxant, anti-oedematous, bronchodilator, and antisnake venom.[23,24,29–31,60–62,65,66]

The biological effects of *M. glomerata* and *M. laevigata*

Medicinal plants and the compounds derived from them are a good source of new and specific inhibitors of the inflammatory process. The past decade has witnessed many important discoveries in this field, with new findings challenging the more traditional views of researchers. In Table 3[67–72] the key papers on the pharmacology of *Mikania* and their scientific findings have been summarized.

Bronchodilator activity

Obstructive airway diseases, in which asthma is included, show a variety of symptoms. Physiologically they are characterized by maximal expiratory flow limitation, and pathologically by inflammation of the airways and the lung parenchyma. Inflammation plays a major role in the gradual aggravation of the lung function resulting in worsening symptoms.[73] Studies are in progress to identify various molecular targets in these pathways for the purpose of

Table 2 Bioactive constituents of *Mikania laevigata* and *Mikania glomerata*

Reference	Biological activity	Bioactive constituents
Oliveira *et al*.[17]	Antimicrobial and anti-ulcerogenic, antispasmodic and anti-inflammatory	Kaurenoic acid, grandifloric acids, stigmasterol, coumarin and dihydrocoumarin
Yatsuda *et al*.[39]		
Davino *et al*.[59]		
Lucas *et al*.[24]	Expectorant action of the plant	Coumarin glycoside
Bighetti *et al*.[60]	Gastric antisecretory activity mediated by the parasympathetic system	The coumarin and the crude hydroalcoholic extract of *M. Laevigata*
Alves *et al*.[31]	Anti-inflammatory	The coumarin and the crude hydroalcoholic extract of *M. laevigata*
Booth *et al*.[61]	Anticoagulant effect	1,2-Benzopyrone
Santos *et al*.[23]	Anticoagulant effect	Coumarin and o-coumarin
Pedroso *et al*.[49]	Stimulated docosahexaenoic acid synthesis in the liver	Coumarin and o-coumarin
Pereira *et al*.[62]	Anti-*B. jararaca* venom	Coumarin
Born *et al*.[63]	Rat liver toxicant	Coumarin
Ulubelen *et al*.[64]	Antifertility activity in mature female rats	Coumarin

Table 3 Key papers on the pharmacology of *Mikania* and their scientific findings

Reference	Key papers and their scientific findings
Fierro *et al*.[28]	Ethanolic extract of *M. glomerata* reduced pleural oedema
Silva *et al*.[67]	Ethanolic extract of *M. glomerata* inhibited pleural eosinophilia
Soares-de-Moura *et al*.[29]	Extracts of *M. glomerata* were active on respiratory smooth muscle
dos Santos *et al*.[23]	Hydroalcoholic extract of *M. laevigata* decreased significantly the influx of leucocytes, especially eosinophils, to the bronchoalveolar space
Graça *et al*.[68]	Hydroalcoholic extract from *M. laevigata* induced a concentration-dependent relaxation of rat trachea which does not depend on epithelium-derived substances but involves changes in the cellular mobilization of calcium
Freitas *et al*.[26]	Extracts of *M. glomerata* and *M. laevigata* diminished lung inflammatory infiltration induced by coal dust
Alves *et al*.[31]	The anti-neutrophil migration effects of extract from *M. laevigata* were associated with nitric oxide expression dependent on iNOS activation and also inhibition of the production of cytokines and consequently neutrophil migration
Bighetti *et al*.[60]	Hydroalcoholic extract of *M. laevigata* decreased the ulcerative lesion index produced by indometacin, ethanol, stress and reserpine in rats, as well as decreasing the hydrogen ion concentration
Do Amaral *et al*.[58]	Hexanic extract of *M. glomerata* presented antibacterial activity against a multiresistant strain of *Staphylococcus aureus*
Holetz *et al*.[1]	Ethanolic fraction of *M. glomerata* presented only weak activity against both Gram-positive and Gram-negative bacteria
Yatsuda *et al*.[39]	The crude extracts of both *Mikania* did not show bactericidal activity against most of the clinical isolates. Ethyl acetate fractions of both *Mikania* displayed negligible effects against mutans streptococci. On the other hand the ethanolic extracts inhibited the growth of all microorganisms tested and the hexane fraction of both species of *Mikania* showed remarkable antibacterial activity
Barratto *et al*.[69]	The ethanolic extract of *M. laevigata* presented significant antimicrobial activity against *S. aureus*, *E. coli*, *P. aeruginosa*, *E. faecalis* and *E. faecium*
Betoni *et al*.[70]	Synergism of plant extract with antibiotics. *M. glomerata* presented synergistic effect with antimicrobial drugs against *S. aureus*
Holetz *et al*.[1]	Hydroalcoholic extract of *M. glomerata* had a moderate activity against *Candida* species
Duarte *et al*.[54]	Extract of *M. glomerata* was not effective at any of the concentrations tested against *C. albicans*
Luize *et al*.[71]	Extract of *M. glomerata* demonstrated 97.5% growth inhibition against amastigote forms of *L. amazonensis*, as well as 49.5% of growth inhibition of epimastigote forms of *T. cruzi*
Maiorano *et al*.[66]	Phospholipase A_2 activity induced by *Crotalus durissus terrificus* venom was totally inhibited by the aqueous extracts of *M. glomerata*, while for *Bothrops jararacussu* venom no significant inhibition was observed
Da Silveira e Sá *et al*.[72]	*M. glomerata* ethanolic extract does not interfere with the fertility in rats
Graça *et al*.[68]	*M. laevigata* syrup presented no adverse effects on the spermatogenic process as well no toxicity in the hepatic, renal or pancreatic systems
Soares-de-Moura *et al*.[29]	*M. glomerata* extract fraction is devoid of genotoxicity since this fraction did not damage DNA either directly or by producing reactive oxygen species

developing novel therapeutic approaches. In this context, natural agents have been used in numerous cultures for the treatment of several medical conditions and have mostly proven to be safe.

Bronchoconstriction plays a very important role in the physiopathology of asthma, and compounds that relax respiratory smooth muscles such as β2-agonists, theophylline and cholinergic antagonists are usually used in symptomatic treatment of the disease. *M. laevigata* and *M. glomerata* are traditionally used to treat respiratory illness in Brazil. The 'guaco' leaves are commonly used as an extract, syrup or infusion to treat bronchitis, asthma and cough.[17] Experimental observations of the efficacy of 'guaco' use in airway diseases have been consistent, and some studies demonstrated the mechanisms of its action.

Fierro *et al*.,[28] using a model of allergic pleurisy in rats, demonstrated that the animals treated with a fraction obtained from the ethanolic extract of *M. glomerata* had a reduction of pleural oedema at the highest dose tested, as well inhibition of leucocyte infiltration detected after antigen challenge. Interestingly, the ethanolic extract of *M. glomerata* inhibited pleural eosinophilia, and this process is dependent on eicosanoids and platelet-activating factor.[67] One possible explanation for the inhibitory effect of ethanolic extract of *M. glomerata* on rat allergic pleurisy is that it antagonizes the effects and/or the release of this lipid although there is no inhibitory activity on pleurisy triggered by histamine or serotonin.[28] Another study demonstrated that the hydroalcoholic extract of *M. glomerata* produced a decrease of the basal tonus of the isolated respiratory smooth muscle of the guinea-pig trachea. When the respiratory smooth muscle was contracted with histamine, acetylcholine or high K^+, in the presence of diverse pharmacological agents such as propranolol, atropine, mepyramine or L-NAME, the presence of hydroalcoholic extract of *M. glomerata* induced a significant concentration-dependent relaxation. This suggested that the inhibitory effect of *M. glomerata* was not dependent on inhibition of muscarinic or histaminergic receptors, activation of β2-adrenoceptors, release of nitric oxide and/or prostanoids or activation of K^+ channels. Furthermore, the vasodilator effect was lower than the bronchodilator effect of the hydroalcoholic extract of *M. glomerata*. This suggested that the compounds present in

the extracts of *M. glomerata* were more active on the respiratory smooth muscle than on vascular smooth muscle. Thus, the probability of a large reduction in arterial blood pressure would appear to be remote.[29]

Regarding *M. laevigata*, dos Santos *et al*.[23] used a mouse model of allergic pneumonitis to demonstrate that the animals treated with the hydroalcoholic extract of *M. laevigata* had significantly decreased influx of leucocytes, especially of eosinophils, to the bronchoalveolar space. Further, the analyses of histopathological images demonstrated a haemorrhagic profile in the lung tissue of the untreated animals which was not observed in the animals treated with hydroalcoholic extract.

Another study was conducted to investigate the efficacy of a hydroalcoholic extract of the aerial parts of *M. laevigata* as a relaxant agent in tracheal smooth muscle *in vitro*.[68] The authors used acetylcholine to induce a sustained contraction of the rat tracheal smooth muscle, which was fully relaxed when the hydroalcoholic extract of *M. laevigata* was added. This action was not dependent on epithelium-derived substances as the antagonists nitric oxide and guanylate cyclase, both important regulatory mediators in airway function, did not abolish tracheal relaxation elicited by the hydroalcoholic extract of *M. laevigata*. On the other hand, the action was largely dependent upon activation of tetraethylammonium-sensitive (but not glibenclamide- or 4-aminopyridine-sensitive) potassium channel blockers, suggesting that the direct stimulation of calcium-activated potassium channels by *M. laevigata* extract may have contributed to the underlying mechanism by which *M. laevigata* acted as an anti-asthmatic phytomedicine in humans.[68]

Pneumoconiosis is a respiratory disease characterized by pulmonary inflammation caused by coal dust exposure, inducing an aggregation of macrophages near the respiratory bronchioles responsible for the formation of reactive oxygen species.[74] Considering that coal dust exposure induces an inflammatory response in lungs and that *M. glomerata* and *M. laevigata* are plants used in Brazilian folk medicine for several inflammatory conditions of the respiratory system, Freitas *et al*.[26] investigated whether extracts from these plants presented any effect on inflammatory and oxidative damage indicators in the lungs of rats acutely exposed to coal dust. The authors observed that lactate dehydrogenase activity was increased by coal dust intratracheal instillation, suggesting that coal dust exposure induced cellular death. *M. laevigata* extract pretreatment prevented this effect, but *M. glomerata* extract did not. Furthermore, total cell count was increased in coal dust-exposed rats and both extracts inhibited the increase in cell count. These results gave evidence that coal dust led to inflammation and cellular death in lungs of rats and that *M. laevigata* presented a protective effect in these parameters. Besides, coal dust induced oxidation of sulfhydryl groups, since protein thiol content was significantly decreased in the lungs of the animals. *M. glomerata* extract and *M. laevigata* extract prevented this effect, leading to speculation that these extracts may present a protective role in oxidation of thiol groups caused by coal dust acute exposure.[26]

In summary, both *M. glomerata* and *M. laevigata* have been shown to possess efficient anti-asthmatic activity, confirming their traditional popular use for respiratory diseases.

Anti-inflammatory activity

The inflammatory response is orchestrated by a large range of mediators able to promote vascular events, oedema and recruitment of inflammatory cells. In response to injury or infection, the body mobilizes cells of the immune system to initiate an inflammatory response at the site of damage. A critical step in this response is the adhesion of circulating leucocytes to the endothelial cells lining the blood vessels, allowing their subsequent migration across the endothelial cell barrier to access the insult.[75]

As stated above, *M. glomerata* extract is largely used to treat respiratory disease, however the beneficial effects of *M. glomerata* in the treatment of respiratory disease such as asthma may not only comprise a direct relaxation of the respiratory smooth muscle but also an anti-inflammatory effect. In this context, some studies demonstrated the anti-inflammatory activity of *Mikania* extracts.

Recently, Alves *et al*.[31] assessed the pharmacological properties and the underlying molecular mechanisms of the hydroalcoholic extract of *M. laevigata*, to corroborate the popular wisdom of it being a putative anti-inflammatory drug. The authors observed an anti-inflammatory effect of *M. laevigata* extract on carrageenan-induced peritonitis in mice, since the 'guaco' extract reduced neutrophil migration and vascular permeability in this animal model. However, to be a good candidate for an anti-inflammatory drug with commercial advantages, the chemical composition must not be influenced by the season of collection. Thus, additional data was provided, demonstrating that all monthly harvested 'guaco' extracts similarly inhibited neutrophil migration as compared with carrageenan-injected mice, and no statistical significance was detected among the analysed months.[31]

To understand the molecular mechanism by which the hydroalcoholic extract of *M. laevigata* exerted its anti-inflammatory activity, Alves *et al*.[31] performed several experiments. The findings clearly demonstrated that treatment with hydroalcoholic extract of *M. laevigata* strikingly prevented the release of both tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in response to carrageenan injection. The inhibition of cytokine expression contributed to a reduction in leucocyte adhesion and transmigration across the endothelium, as observed by intravital microscopy.[31] It is important to point out that the expression of surface molecules on the vascular endothelium allowing the leucocytes to diapedesis was influenced by the cytokine milieu in which the endothelial cells resided. Furthermore, pretreatment of mice with aminoguanidine followed by 'guaco' administration completely abrogated the suppression of neutrophil migration into mesenteric postcapillary venules and increased nitrite content. These findings indicated that nitric oxide (NO), produced via inducible nitric oxide synthetase (iNOS) activation, was associated with the suppression of neutrophil migration caused by 'guaco' extract.[31] Thus, taken together, the results suggested that use of the medicinal 'guaco' extract may have been able to suppress the development of acute inflammatory lesions, which were initiated by neutrophil recruitment.

Another interesting result obtained with *M. laevigata* extract was demonstrated in an inflammatory periodontal disease model induced by a ligature placed around the mandible first molars of animals. Morphometrical analysis of alveolar bone loss demonstrated that guaco-treated animals presented a decreased alveolar bone loss and a lower expression of the activator of nuclear factor-κB ligand (RANKL) measured by immunohistochemistry. Moreover, gingival tissues from the guaco-treated group showed decreased neutrophil migration (myeloperoxidase assay). These results indicated that 'guaco' extract may have been useful to control bone resorption during progression of experimental periodontitis in rats (unpublished data).

Anti-ulcerogenic activity

Gastric and duodenal ulcers affect a great number of people worldwide and are caused by multiple factors such as stress, smoking, nutritional deficiencies and ingestion of nonsteroidal anti-inflammatory drugs.[76] The current treatment has its problems due to the limited effectiveness and severe side effects of the available drugs. Protection of the gastric mucosa involves acid-pepsin secretion, parietal cell activity, mucosal barrier, mucus secretion, blood flow, cell regeneration, and the release of endogenous protective agents, especially prostaglandins and epidermal growth factors. Numerous approaches have been used to combat gastric ulcers, including the control of acid secretion, *Helicobacter pylori* level, and H^+/K^+-ATPase activity, in an attempt to reverse mucosal damage and inflammation.[77] The use of natural products for the prevention and treatment of different pathologies is continuously expanding throughout the world. In this context, extracts and active principles from plants could serve as leads for the development of new drugs.[78]

Bighetti *et al*.[60] evaluated the anti-ulcerogenic activity of *M. laevigata* extract, employing different experimental models in rats, to discern the pharmacological mechanism of action, such as: the indometacin-induced ulcer model, which is used to show cytoprotection and gastric acid secretion effects; the ethanol-induced ulcer model, used to screen drugs for cytoprotection; high reserpine doses which produce an intense generalized discharge of sympathetic nervous system mediators, inducing ulcers within 24 h; and a stress model, with ulcers induced by immobilization at low temperatures.[79–81] The crude hydroalcoholic extract (1000 mg/kg) decreased the ulcerative lesion index produced by indometacin, ethanol, stress and reserpine in rats by 85, 93, 82 and 50%, respectively. Besides, in the pyloric ligation model a decrease of hydrogen ion concentration (53%) was observed, suggesting that the pharmacological mechanism had a relationship to antisecretory activity. Furthermore, the authors used several drugs to block specific receptors to evaluate the mechanism by which the extract of *M. laevigata* was inhibiting the ulcer lesions. The blockage of the anti-ulcerogenic activity of the extract of *M. laevigata* promoted by bethanechol suggested an anticholinergic mechanism or an interruption of intracellular events that were linked to acid secretion.[60]

Antimicrobial activity

Infectious diseases still represent an important cause of morbidity and mortality among humans, especially in developing countries. Even though the pharmaceutical industry has produced a number of new antimicrobial drugs in the last few years, resistance to these drugs by microorganisms has increased. Conventional medicine is increasingly receptive to the use of antimicrobial and other drugs derived from plants as traditional antibiotics (products of microorganisms or their synthesized derivatives) become ineffective and as new, particularly viral, diseases remain intractable to this type of drug. Another driving factor for the renewed interest in plant antimicrobials over the past 20 years has been the rapid rate of (plant) species extinction.[82] Newmman and Cragg[4] related that with regards to antibacterial compounds, 76.5% of the new chemical entities were related to natural products. In this context, the *Mikania* genus also presents some antibacterial effects. Thus some studies concerning the antibacterial activity of *M. laevigata* and *M. glomerata* were analysed.

Antibacterial activities of different polarities of *M. glomerata* extracts were evaluated against a multiresistant strain of *Staphylococcus aureus* PI57. Only in the hexanic extract of *M. glomerata* were substances with antibacterial activity detected, since the ethanolic and dichloromethane extracts did not present antibacterial activity.[58] Another study evaluating different fractions of *M. glomerata* extract demonstrated that the ethanolic fraction presented some degree of activity (weak) against Gram-positive and Gram-negative bacteria. In this study it was necessary to use a considerable concentration of the ethanolic extract of *M. glomerata* to inhibit *Staphylococcus aureus* (500 μg/ml), Bacillus subtilis (250 μg/ml), *Escherichia coli* (500 μg/ml) and *Pseudomonas aeruginosa* (>1000 μg/ml).[1]

Yatsuda *et al*.[39] evaluated the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of different fractions of the extracts from *M. laevigata* and *M. glomerata*, such as ethanolic extracts (EE), hexane fractions (H) and ethyl acetate fractions (EA). They demonstrated that EA from both *Mikania* species displayed negligible effects against mutans streptococci. The ethanolic extracts inhibited the growth of all microorganisms tested, except the strains of *Streptococcus mutans* D1 and *Streptococcus mutans* P6. However, the crude extracts of both *Mikania* did not show bactericidal activity against most of the clinical isolates. In contrast, the hexane fraction of both species of *Mikania* showed remarkable antibacterial activity, displaying the lowest MIC (12.5–100 mg/ml) and MBC (12.5–400 mg/ml) values. Furthermore, the extracts and fractions of *M. laevigata* and *M. glomerata* were able to inhibit the adherence of mutans streptococci cells to a glass surface at sub-MIC levels and the hexane fractions were the most effective agents.[39] Baratto *et al*.[69] demonstrated that none of the ethanolic extracts of *M. laevigata* presented significant antimicrobial activity against *S. aureus* (25923), *E. coli* (25992), *P. aeruginosa* (27853), *Enterococcus faecalis* (29212) and *Enterococcus faecium* (10541).

Another interesting approach is the study of the synergism of the mechanism of action of the plant extract with antibiotics or with other medicinal plants. In a study conducted by Betoni *et al*.[70] the synergism between 13 antimicrobial drugs and eight plant extracts, including the *M. glomerata* extract, was verified. The antimicrobial mechanisms of the drugs used were variable and the protein

synthesis inhibitors were those that presented the strongest synergistic effect (5.2 extracts per drug), together with folic acid (4 extracts per drug) and bacterial cell wall synthesis inhibitors (3.8 extracts per drug). Inhibitors of nucleic acid synthesis resulted in two extracts per drug. The *M. glomerata* extract presented a synergistic effect with seven antimicrobial drugs against *S. aureus*. There were three protein synthesis inhibitors (tetracycline, chloramphenicol and netilmicin) and four bacterial cell wall synthesis inhibitors (gentamicin, vancomycin, penicillin and cephalothin). Therefore, the results of the study seemed to be promising and may enhance the natural product's uses, showing the potential of the *M. glomerata* extract in the treatment of infectious diseases caused by *S. aureus*.

Candida albicans is an opportunistic pathogen that can cause local and systemic infections in predisposed persons, commonly affecting immunologically compromised patients and those undergoing prolonged antibiotic treatment.[83] According to the literature, the investigation of natural products active against *Candida* spp. increased significantly in the last 10 years, with the investigation of approximately 258 plant species, from 94 families. Holetz *et al*.[1] observed that the hydroalcoholic extract of *M. glomerata* had a moderate activity against *C. krusei* (500 μg/ml) and *C. tropicalis* (500 μg/ml) and a weak activity against *C. albicans* (>1000 μg/ml). Corroborating those results, the ethanolic extract of *M. glomerata* was not effective at any of the concentrations tested against *C. albicans*.[54] On the other hand, the authors observed a strong activity against *C. albicans* for oils of *M. glomerata* at levels of 0.25 μg/ml.

Antiparasitic activity

Trypanosoma cruzi is an intracellular protozoan which causes Chagas disease. Endemic to several regions in Latin America, this disease persists as the major infectious heart disease in the world. It is estimated that approximately 75 million people live in risk areas and 13 million people are currently infected in Central and South America. The global incidence of the disease is considered to be 300 000 new cases per year.[84] The therapeutic options currently available for Chagas disease are limited. Most of the therapeutic measures are aimed at treating the consequences of the disease such as cardiac failure.

Leishmaniasis, caused by the intracellular protozoan parasite of mononuclear phagocytes *Leishmania*, is endemic in 88 countries. *Leishmania amazonensis*, a species transmitted mainly in the Amazon region, has been associated with localized cutaneous lesions, diffuse cutaneous disease, and mucosal infection. The disease is neglected by the pharmaceutical industry, even though no vaccine exists, and significant side effects and signs of increasing resistance continue to occur with the use of the few effective drugs available.[85]

The immense chemical diversity and range of bioactivity of plants has led to the development of hundreds of pharmaceutical drugs. Luize *et al*.[71] reported the results of preliminary screening tests for trypanocidal and leishmanicidal activities of crude extracts from 19 plants used in Brazilian folk medicine for the treatment of various diseases. Regarding *M. glomerata*, the results obtained demonstrated 97.5% growth inhibition against amastigote forms of *L. amazonensis*, as well as 49.5% growth inhibition of epimastigote forms of *T. cruzi*. Furthermore, *M. glomerata* extract did not show any haemolytic effect on sheep blood.[71]

Antiophidian properties

Envenomation by snakes is often treated by parenteral antiophidian serum administration, obtained from hyperimmunized equine serum. Vegetal extracts constitute an excellent alternative source of novel antiophidian agents. In many countries, vegetal extracts have been traditionally used in the treatment of envenomations evoked by snakebites. Maiorano *et al*.[66] evaluated the ability of aqueous extracts, from extract of *M. glomerata*, to inhibit pharmacological and enzymatic activity of *Bothrops* and *Crotalus* snake venoms. The results obtained demonstrated that phospholipase A2 activity induced by *Crotalus durissus terrificus* venom was totally inhibited by the aqueous extracts of *M. glomerata*, while, for *Bothrops jararacussu* venom, no significant inhibition was observed. *M. glomerata* extract also inhibited the haemorrhagic activity of the venoms tested, suggesting an interaction between the extract components and metalloproteases, involving catalytic sites of these enzymes or essential metal ions. Also, *M. glomerata* extract exhibited powerful inhibition of the clotting activity, probably due to interaction with thrombin-like enzymes.[66]

Impact of *Mikania* extracts on reproductive organs

The plants of the genus *Mikania* contain many active compounds that may be related to its different therapeutic properties according to folk medicine. Two of these compounds, flavonoids and coumarin, have been reported to affect the fertility of the male dog and female rat, respectively, in experiments carried out using other plant genera.[64,86] Flavonoids and coumarin are among the constituents of *M. glomerata* and *M. laevigata*, with coumarin being one of the main active substances from the leaves of this species.[39]

Previous studies have demonstrated that the long-term (52 consecutive days) administration of the ethanolic extract of the aerial parts of *M. glomerata* did not interfere with fertility in rats.[72] In that study, the authors administered the extract at a dose level of 3.3 g/kg, which was 600-times higher than the human dose. Despite the long-term and high-dose treatment, the results showed nontoxicity of the *M. glomerata* extract as well as no alteration in androgen or sperm production, and sperm morphology remained unaltered in the extract-treated animals.[72] Furthermore, in another study in which animals were treated daily with *M. laevigata* syrup over 90 days by oral gavage, there were no alterations in body or organ weights, and no alteration in sperm and spermatid numbers, or in sperm morphology of the male rats, suggesting the absence of adverse effects on the spermatogenic process.[68]

Toxicity and genotoxicity

Plants have been used for centuries to treat infections and other diseases in humans, but controlled clinical studies have

been scarce. In some cases, popular wisdom together with research has meant that records have begun to be kept for the safety and effectiveness of phytochemical treatments, but these are generally uncontrolled and nonrandomized studies.

The oral and intraperitoneal acute toxicity of *M. laevigata* syrup, containing controlled amounts of coumarin, have been assessed, as well as the oral subchronic and chronic toxicity. The calculated LD50 (lethal dose 50%) of *M. laevigata* syrup after intraperitoneal administration was 0.904 g/kg in mice (both sexes) and 0.967 and 0.548 g/kg in male and female rats, respectively. However, the LD50 value of *M. laevigata* syrup by the oral route was calculated to be up to 10 g/kg, in both male and female mice and rats. Repeated dose 28- or 90-day oral treatment with *M. laevigata* syrup (75, 150 and 300 mg/kg) did not produce any disturbances in the haematological or biochemical parameters of either male or female rats, nor did it provide evidence of toxicity in the hepatic, renal or pancreatic systems.[68] Furthermore, Alves *et al*.[31] demonstrated the absence of effects on body weight gain and behavioural patterns in mice subjected to the repeated-dose 14-, 28- or 60-day treatment, indicating no relevant toxicity induced by *M. laevigata* ethanolic extract in mice. Besides, there were no alterations in haematological parameters or serum aminotransferases (AST and ALT), indicative of normal hepatic and biliary function, lack of liver cell injury, and no alterations in urea, indicating the absence of alterations in the kidney. Thus, the pharmacological concentration used in this study (3 mg/kg) presented no toxicity. Also, the LD50 was found to be almost 75-times higher than the pharmacological dose tested.

The potential genotoxicity of *M. glomerata* extract fraction performed on plasmid DNA using an alkaline lysis procedure was evaluated, in which plasmid DNA was treated with SnCl2 and *M. glomerata* extract fraction. The role of reactive oxygen species in DNA breakage was evaluated also, by incubating *M. glomerata* extract fraction with sodium benzoate, a hydroxyl radical scavenger. The results have shown that *M. glomerata* extract fraction was devoid of genotoxicity, since this fraction did not damage DNA either directly or by producing reactive oxygen species (at least the hydroxyl radical).[29] Another important criterion in the search for compounds active against microorganisms with therapeutic potential, is to determine whether they show toxic effects on mammalian host cells. For this purpose, Luize *et al*.[71] carried out a cytotoxicity test on sheep erythrocytes to determine the ratio of selectivity to biological activity. No haemolytic effects of the crude extract of *M. glomerata* on sheep blood were observed after 60-min incubation.

Conclusions

In recent years interest in phytomedicine has increased. In Brazil, there is a national policy to increase the use of phytomedicine for the treatment of some diseases, and 'guaco' syrup has been available since 2006, mainly indicated for respiratory conditions. *M. laevigata* Schultz Bip. ex Baker and *M. glomerata* Spreng are the two medicinal plants in Brazil that are used interchangeably and often at times with no distinction between the two species. Phytochemical studies of the leaves from *M. laevigata* and *M. glomerata* species indicated a similar composition; presenting diterpene acids (ent-kaurene derivatives); triterpenes and steroids (friedelin, stigmasterol and lupeol) and cinnamic acid derivatives as well coumarins, diterpenes, and essential oils. However, the amounts of these chemical compositions were different. Both *Mikania* species possess immunomodulatory activity, reducing oedema formation as well as neutrophil migration in part dependent on the nitric oxide pathway. *M. laevigata* and *M. glomerata* are used traditionally to treat respiratory illness in Brazil. The 'guaco' leaves are commonly used as an extract, syrup or infusion to treat bronchitis, asthma and cough. Experimental observations about the efficacy of 'guaco' usage in airway diseases are consistent, and some studies have demonstrated the mechanisms of its action.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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