



MIKANIA GLOMERATA AS A PHARMACOLOGICAL TOOL

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<https://doi.org/10.5281/zenodo.6514294>

ARTICLE INFO

Received: 20th April 2022

Accepted: 25th April 2022

Online: 30th April 2022

KEY WORDS

guaco, *anti-infective*,
mikania

ABSTRACT

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.

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. 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 bio-active 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.

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-infective. 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 Cragg⁴ 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 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 focused 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. The genus is widely distributed in Brazil with approximately 171 described species, with approximately 150 of these being endemic, including *M. laevigata*.

Mikania grows as a timbered shrub with a branched cylindrical stem. This plant is a

sub-scrub creeper of woody branches and brilliant-green leaves that release a strong aroma reminiscent of vanilla. The species are characterized by their capitula which are composed of four florets and involucre 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 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* DCM. *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.

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. *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. 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.

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. 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.

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 reduce pleural oedema, showing anti-allergic activity at the highest dose tested. The administration of a dichloromethane fraction dose-dependently inhibited leucocyte infiltration detected after antigen challenge. Experiments have demonstrated an anti-allergic effect of a dichloromethane fraction obtained from the hydroalcoholic extract of *M. glomerata* leaves in rats.²⁸ The 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. Chromatographic studies performed with the dichloromethane fraction confirmed the findings of Lucas and Oliveira 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.* 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-inflammatory action of *M. glomerata* as demonstrated by Ruppelt

Duarte 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. Yatsuda 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 dichloromethane extracts did not present antibacterial activity, and were detected only in the hexanic extract of *M. glomerata* substances with

antibacterial activity. 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.

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. 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.

Conclusion. 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.

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