Atividades de Ensino e de Pesquisa em Química 3

Jéssica Verger Nardeli
(Organizadora)

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APRESENTAÇÃO

A coleção “Atividades de Ensino e de Pesquisa em Química” é uma obra que tem um conjunto fundamental de conhecimentos direcionados a industriais, pesquisadores, engenheiros, técnicos, acadêmicos e, é claro, estudantes. A coleção abordará de forma categorizada pesquisas que transitam nos vários caminhos da química de forma aplicada, inovadora, contextualizada e didática objetivando a divulgação científica por meio de trabalhos com diferentes funcionalidades que compõem seus capítulos.

O objetivo central foi apresentar de forma categorizada e clara estudos relacionados ao desenvolvimento de protótipo de baixo custo, análise do perfil químico de extratos, degradação de resinas, quantificação de flavonoides, estudo de substâncias antioxidantes e avaliação do grau de contaminação das águas. Em todos esses trabalhos a linha condutora foi o aspecto relacionado ao desenvolvimento, otimização e aplicação, entre outras abordagens importantes na área de química, ensino e engenharia química. Atividades de Ensino e de Pesquisa em Química 3 tem sido um fator importante para a contribuição em diferentes áreas de ensino e pesquisa.

Temas diversos e interessantes são, deste modo, discutidos aqui com a proposta de fundamentar o conhecimento de acadêmicos, mestres e todos aqueles que de alguma forma se interessam pela área de química. Possuir um material que demonstre evolução de diferentes metodologias, abordagens, aplicações de processos, caracterização substanciais é muito relevante, assim como abordar temas atuais e de interesse tanto no meio acadêmico como social.

Portanto, esta obra é oportuna e visa fornecer uma infinidade de estudos fundamentados nos resultados experimentais obtidos pelos diversos pesquisadores, professores e acadêmicos que desenvolveram seus trabalhos que aqui serão apresentados de maneira concisa e didática.

Jéssica Verger Nardeli

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CAPÍTULO 8

PLANTAS MEDICINAIS COM EFEITOS ANTITUSSÍGENOS E EXPECTORANTES COMO FONTE DE TRATAMENTO RESPIRATÓRIO: UMA REVISÃO

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ABSTRACT: *Mikania glomerata* is a medicinal plant that has pharmacological activities, which include antiallergic, antimicrobial, analgesic, anti-inflammatory, antioxidant activities, among others. *Hedera helix* acts to combat secretory, mucolytic and expectorant diseases. For *Pelargonium sidoides* it is used to treat respiratory tract infections. The study aims to review the plants *Mikania glomerata, Hedera helix* and *Pelargonium sidoides* used in the treatment of respiratory tract diseases, useful for future research in the development of new herbal medicines. A bibliographic research was carried out with 56 articles found in Scopus, Web of Science, Academic Google, SciELO, ANVISA and Ministry of Health databases from 2006 to 2019. The articles were analyzed from the title, content and text, referring to the studies that involves the use of herbal medicines for the treatment of respiratory diseases. The plants under the study demonstrated their efficacy in treatment and cure of the respiratory diseases. The analyzed publications had greater coverage for the *Hedera helix* L. plant in the year 2016. The ease of obtaining the plants and their less side effects has provided safety for the treatment of many respiratory diseases, such as asthma, bronchitis, reflux, sinusitis, tuberculosis, among others, allowing to attenuate or even eliminate diseases.
KEYWORDS: Antitussive, *Hedera helix*, *Mikania glomerata*, *Pelargonium sidoides*, Phytotherapy.

MEDICINAL PLANTS WITH ANTITUSSIVE AND EXPECTORANT EFFECTS AS SOURCE FOR RESPIRATORY TREATMENT: A REVIEW

RESUMO: *Mikania glomerata* é uma planta medicinal que possui atividades farmacológicas, que incluem atividades antialérgicas, antimicrobianas, analgésicas, anti-inflamatórias, antioxidantes, entre outras. *Hedera helix* atua no combate a doenças secretoras, mucolíticas e expectorantes. O *Pelargonium sidoides* é usado para tratar infecções do trato respiratório. O estudo tem como objetivo rever as plantas *Mikania glomerata*, *Hedera helix* e *Pelargonium sidoides* utilizadas no tratamento de doenças do trato respiratório, úteis para futuras pesquisas no desenvolvimento de novos fitoterápicos. A pesquisa bibliográfica foi realizada com 56 artigos encontrados nas bases de dados Scopus, Web of Science, Academic Google, SciELO, ANVISA e Ministério da Saúde de 2006 a 2019. Os artigos foram analisados a partir do título, conteúdo e texto, referentes aos estudos que envolvem o uso de fitoterápicos no tratamento de doenças respiratórias. As plantas estudadas demonstraram sua eficácia no tratamento e cura de doenças respiratórias. As publicações analisadas apresentaram maior cobertura para a planta *Hedera helix L.* no ano de 2016. A facilidade de obtenção das plantas e seus menores efeitos colaterais tem proporcionado segurança para o tratamento de muitas doenças respiratórias, como asma, bronquite, refluxo, sinusite, tuberculose, entre outras, permitindo atenuar ou mesmo eliminar doenças.
PALAVRAS-CHAVE: Antitússico, *Hedera helix*, *Mikania glomerata*, *Pelargonium sidoides*, Fitoterapia.

1 | INTRODUCTION

Herbal or herbal medicines are defined through preparations with therapeutic benefits, in the treatment and cure of diseases (Ghazali et al., 2019). Due to the search for new alternatives for the treatment of diseases, the Ministry of Health implemented the National Policy on Medicinal Plants and Herbal Medicines (PNPMF) (Brazil, 2006), which brought perspectives for curing diseases through the use of medicinal plants.

The use of alternative practices as an option for health care led to the use of herbal medicines (Rezende & Cocco, 2002), opting for the use of plants with medicinal effects, mainly because they have fewer side effects. Its activities and compositions are well known and proven by scientific studies (Pontes et al., 2007).Among the thousands of species of medicinal plants used in antitussive and expectorant treatment, Mentha piperita stands out, Eucalyptus globulus and Copaifera multijuga stand out, wich have antitussive and expectorant activities (Tavares et al., 2006).

The *Mikania glomerata Spreng.*, is a medicinal plant, belonging to the Asteraceae family, popularly known as guaco, its leaves are used in the treatment of asthma, bronchitis, rheumatic fever and cough (Della Pasqua et al., 2019). It has pharmacological properties, such as antiallergic, antimicrobial, analgesic, anti-inflammatory, antioxidant and antidiarrheal activities (Moreti et al., 2017). Phytochemical studies revealed that is main constituents are coumarin, coumaric acid, sesquiterpenes and diterpenes. The diterpene, ent-caur-16-en-19-oic acid correspond approximately 48.94% of its composition (Moreti et al. 2017). In 1929, *M. glomerata* was recognized by the Brazilian Pharmacopoeia, 1st Edition, and currently, the syrup and the oral solution based on extracts from this plant are provided by the Unified Health System (SUS) (Della Pasqua et al., 2019).

The *Hedera helix* L. is a plant of the family Araliaceae, its fresh leaves and stems are used to treat cough, asthma, bronchitis and other respiratory diseases, which have proved effective in several European countries. This species is registered in the European Pharmacopoeia as herbal medicine (Sun et al., 2016). As a medicament, the plant contains mainly triterpenoid saponins which include hederacoside C, α-hederin, hederacoside B and hederacoside D (Sun et al., 2016). After several studies on H. helix, it was found to be effective as a herbal remedy in the search for cure against secretory, mucolytic and expectorant diseases (Lang et al., 2015).

The *Pelargonium sidoides* DC, belongs to the family Geraliaceae, popularly known as Umckaloabo, and has been used to treat diseases including bronchitis, cough and tuberculosis (Agbabiaka et al., 2008). Commercial phytotherapeutics were formulated from *P. sidoides* tubers because of their ethnobotanical importance (Samie et al., 2019). It is currently marketed as a cough syrup in Germany and is used in the treatment of respiratory infections. In addition, it has been incorporated and marketed in products in South Africa as Flugon® and Linctagon® for similar indications (Aboobaker et al., 2019).

It is worth mentioning that the main constituents isolated from the *P. sidoides* plant were composed of coumarins, simple phenolic structures, as well as flavonoids and catechin derivatives (Schnitzler et al., 2008).

Considering scientific publications on efficacy of *H. helix, M. glomerata* and *P. sidoides* as antitussive and expectorant it is evident that these plants have the potential to prevent, ameliorate or even cure the above mentioned diseases. The objective of this study was to carryout a bibliographic survey of phytotherapeutics that have potential efficacy as antitussive and expectorant in the treatment of respiratory diseases.

2 I MATERIAL AND METHODS

The present study is based on an integrative and literary review, which include articles from periodicals, ANVISA and Ministry of Health websites. The research is bibliographical and exploratory, in a qualitative and descriptive character, carried out from 2006 to 2019, where it searched - filtering information in order to obtain relevant data on the subject, through the use of complete scientific papers. The analysis of approximately 56 articles was performed under three categories: reading the title, abstract and evaluating the full text.

Considering the bibliographical study, the guiding question of the research was: *What are the contributions of phytotherapeutics for the treatment and cure of antitussive and expectorant respiratory diseases?* In order to obtain a better delimitation of the research and a more solid search for the answer of the problem, the articles from 1999 to 2019 were selected from the databases of Scopus, Web of Science, Google Scholar and Scielo, using following keywords: phytotherapics, antitussives, Mikania glomerata, Hedera helix and Pelargonium sidoides.

The inclusion criteria used were based on the study of articles with thematic ones on the use of herbal medicines, the methods used and their effectiveness, written in the Portuguese and English languages. Articles that escaped the above mentioned topic and were in languages other than those suggested were excluded.

3 I RESULTS AND DISCUSSION

Regarding the phytotherapy of respiratory diseases, the study was restricted to three plants, of importance in the treatment of diseases associated with the respiratory system that, consequently cause cough, are: *M. glomerata*, *H. helix* and *P. sidoides*. Among the works evaluated, we found experimental studies in animals, humans and fungi, which met the suggested proposals, finding satisfactory results for the treatment and even the cure of the symptoms associated with cough. According to Table 1, most studies had similar

objectives when analyzing the antitussive and expectorant activities of the administered herbal medicines, as well as their antiviral activity, correlating respiratory diseases.

Of a total of approximately 70 articles that portrayed medicinal, phytotherapeutic and antitussive plants, 56 articles showed the relevance of M. glometara, *H. helix* and *P. sidoides* plants in the treatment of these problems. Among the articles listed in Table 1, most are from experimental studies, usually carried out on rats, all using the studied herbal medicines. Figure 1 shows the number of works published between 2006 and 2019 related to *M. glomerata* researched on the Science Direct website, being in 2017 the year with the highest number of publications on this plant. In figure 2, the data collected are related to *H. helix* the largest number of publication involving this plant was 2016, with a total of 70 articles published. This is probably due to the fact that this plant is a herbal medicine, present in different formulations of pills and syrups (Sun et al., 2016).

For *P. sidoides*, it was found that more than half of the studies related to the use of its leaves for the formulation of a herbal product, its roots already occupied the second position in the analyzed publications. In relation to the year of greatest publications on the manufacture of herbal medicines, it occurred in 2017, with about 12 articles (Figure 03). Several applications of herbal herbal remedies to treat respiratory infections and bronchitis were the most cited, being directly related to symptoms such as cough and sputum.

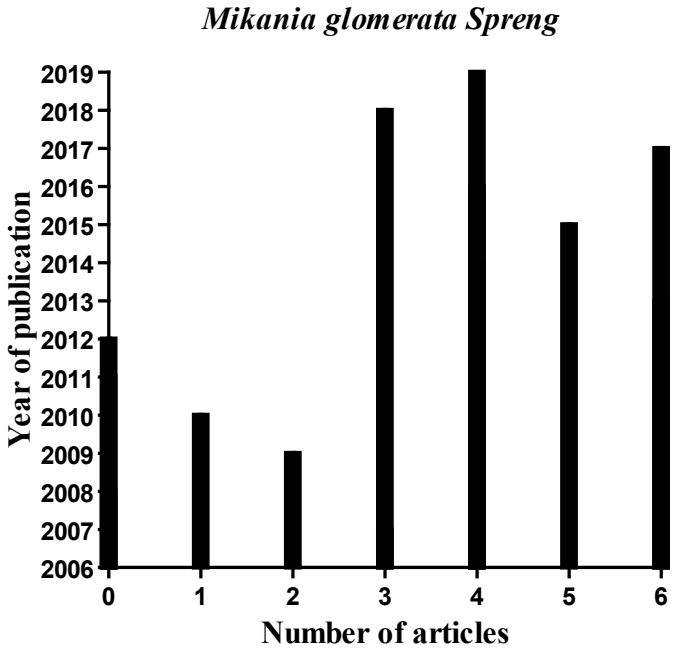

Figure 1. Publications analyzed in the years 2006 to 2019 versus number of published articles of *Mikania glomerata* Spreng.

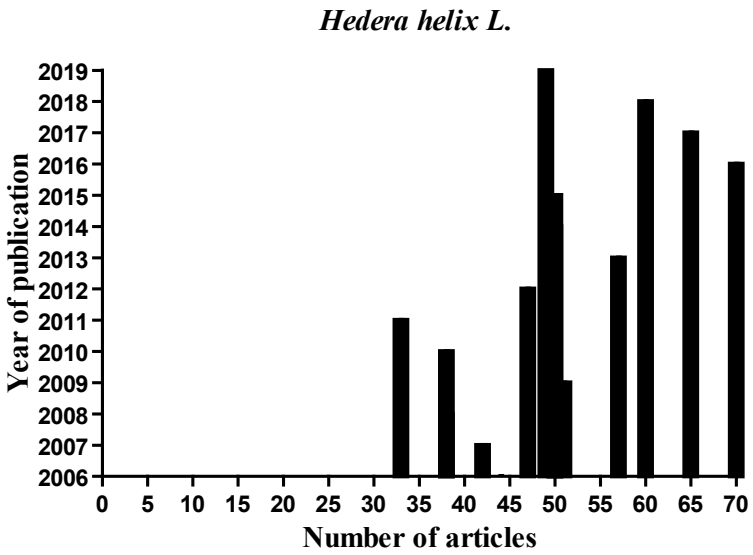

Figure 2. Publications analyzed in the years 2006 to 2019 versus quantity of published articles of *Hedera helix* L.

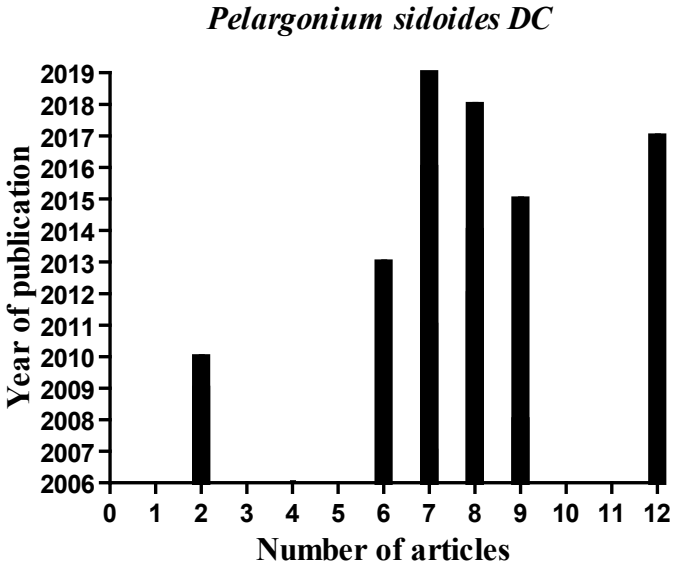

Figure 3. Publications analyzed in the years 2006 to 2019 versus quantity of published articles of *Pelargonium sidoides* DC.

Author / year	Review	Purpose of the study	Plant	Used part	Application	Kind of study
Mello & Mello, 2006	Acta Pharmaceutica Bonaerense	Investigate two herbal formulations using three biological models	*H. helix and M. glomerata*	Extract	Respiratory Tract Infection	Experimental in quail and rats
Santos et al., 2006	Medical Plant	Observe the antiallergic property of the extract and isolated compound from the leaves of *M. glomerata* and *M. leavigata*	*M. glomerata and M. laevigata*	Leaves	Asthma and bronchitis	Experimental model with rats

Soares et al., 2006	Brazilian Journal of Pharmacognosy	Assess toxicology of this preparation in healthy volunteers	*M. glomerata , G. robusta, C. officinalis, M. toluifera, N. officina-le, própolis and mel*	Leaves	Respiratory tract disorders	Experimental model in humans
Tavares et al., 2006	Brazilian Journal of Pharmacognosy	To evaluate the clinical safety of a herbal formulation composed of M. glomerata, M. piperita, E. globulus and C. multijuga, incorporated into propolis and honey.	*M.glomerata, M. piperita, E. globulus and C. multijuga*	Leaves	Respiratory tract disorders	Experimental model in humans
Mativandlela et al., 2006	South African Journal of Botany	To investigate the antifungal, antibacterial and antitubercular activity of *P. sidoides* roots	*P. sidoides*	Root	Tuberculosis	Experimental with bacteria and fungi
Rocha et al., 2008	Brazilian Journal of Pharmacognosy	Transform the *M. glomerata* plant into a quality herbal product safely and effectively proven	*M. glomerata*	Leaves	Respiratory diseases	Experimental model
Freitas et al., 2008	Journal of Medicinal Food	To evaluate the effect of pre-treatment with *M. glomerata* and *M. laevigata* extracts on inflammatory parameters and oxidative stress in rat lungs	*M. glomerata and M. laevigata*	Leaves	Pneumoconiosis	Experimental model in rats
Agbabiaka et al., 2008	Phytomedicine	To evaluate critically the efficacy of *P. sidoides* for the treatment of acute bronchitis	*P. sidoides*	Roots	Acute bronchitis	Review
Gasparetto et al., 2010	Brazilian Journal of Pharmacognosy	Contribute new research in pharmacological, chemical, toxicological, agronomic and genetic	*M. glomerata and M. leavigata*	Leaves, stem and inflorescence	Antiallergic, antiasthmatic, anti-inflammatory	Review
Michaelis et al., 2011	Phytomedicine	Investigate the effects of EPs® 7630 on virus replication (H_1N_1, H_3N_2, H_5N_1)	*P. sidoides*	Roots	Acute bronchitis	Experimental study with cells
Schmidt et al., 2012	Phytotherapy Research	To identify which galenic extract formulation of *H. helix* for the treatment of cough and bronchitis in children	*H. helix*	Leaves	Bronchitis	Experimental model in children
Rufatto et al., 2012	Brazilian Journal of Pharmacognosy	Provide useful references for scientists interested in natural products and research for new compounds	*M. glomerata*	Leaves and stem	Respiratory diseases	Review
Czelusniak et al., 2012	Brazilian Journal of Medicinal Plants	Perform a bibliographic review on the pharmacology, pharmacochemistry and phytochemistry of Guaco	*M. glomerata and M. laevigata*	Leaves	Bronchodilator, antitussive, expectorante	Review

Patiroglu et al., 2012	Phytomedicine	Investigate the efficiency of the P. sidoides extract, as immunomodulatory and antiviral effects, for treatment respiratory	*P. sidoides*	Roots	Respiratory Tract Infection	Experimental model in humans
Santana et al., 2013	Brazilian Journal of Medicinal Plants	To determine the physicochemical properties of the powder obtained from the leaves and evaluate the toxicity in mice	*M. glomerata*	Leaves	Acute toxicity	Experimental model in mice
Timmer et al., 2013	Cochrane Database of Systematic Reviews	To evaluate the efficacy and safety of *P. sidoides* for the treatment of acute respiratory infections	*P. sidoides*	Roots	Treatment of respiratory infections	Review
Hooshyaret al., 2014	Jundishapur J Microbiol	To evaluate the *in vivo* activity of the alcoholic extract of *H. helix* L with experimental zoonotic ulcer of rats	*H. helix*	Leaves	Antileishmanial	Experimental model in rats
Song et al., 2014	Yonsei Med J	To observe the antitussive and expectorant activity of the mixture of extracts *H. helix* and *R. coptidis*	*H. helix and R. coptidis*	Leaves	Antitussive and anti-inflammatory	Experimental model in rats
Song et al., 2014	Biomolecules & Therapeutics	To report the antiviral activity of the ethanolic extract of *H. helix* L	*H. helix*	Leaves	Antiviral	Experimental model with cell cultures
Miyano et al., 2014	Journal of the Brazilian Chemical Society	Development and application of an electrochemical method for the determination of coumarin	*M. glomerata*	Leaves	Effectiveness of coumarins in curing respiratory infections	Electrochemical study
Moyo and Staden, 2014		To know the phytochemistry, pharmacology, toxicology and biotechnology of *P. sidoides*.	*P. sidoides*	Leaves and Roots	Pharmacological	Review
Lang, et al., 2015	Planta med	Carry out a review of leaf extracts in the treatment of inflammatory bronchitis	*H. helix*	Leaves	Bronchitis	Rewiew
Hong et al., 2015	Plos one	To observe the antitussive and antiviral activity of the leaf extract of *H. helix* L	*H. helix*	Leaves	Influenza A	Experimental model in rats
Sun et al., 2016	Plant Physiology and Biochemistry	Observe the biosynthesis of triterpenic saponins in *H. helix* and verify the reliability of reference genes	*H. helix*	Root, stem, leaf, petiole and shoot tip	Identification and validation of reference genes for quantitative purposes	Real-time quantitative reverse transcription (RT-qPCR)
Wu et al., 2017	Pharmacological Research	Discovery of new small molecules for the induction of autophagy	*H. helix*	Ethyl acetate fraction of the ethanolic extract	Protein degradation of neurodegenerative diseases	MPTP Mice

Zdarta et al., 2017	Ecotoxicology and Environmental Safety	Investigate the effects of extract of *H. helix* on the properties of the environmental strain *Raoultella ornithinolytica*	*H. helix*	Leaves and husks	Bioremediation in Raoultella, ornithymolytic properties	Bacterial culture
Moreti *et al.*, 2017	Anaerobe	Display activity against bacteria present in endodontic infections	*M. glomerata*	Dry aerial parts	Antibiofilm and antimicrobian activity	Time maturity tests
Blom Van Staden et al., 2017	South African Journal of Botany	Stimulate tyrosinase activity, induce melanin production and inhibit the growth of Propionibacterium acnes.	*P. sidoides*	Leaves and branches	Antibacterial activity against *Propionibacterim acnes*	Mice
Zaiter *et al.*, 2018	Microchemical Journal	Antioxidant activity, bioactive compounds identified and quantified	*H. helix*	Leaves	LC-PDA-ESI / MS Techniques	UV spectrophotomtry, DPPH elimination test
Possebon et al., 2018	Biomedicine & Pharmacotherap	To evaluate the therapeutic potential of *M. glomerata*	*M. glomerata*	Fresh leaves	Anti-inflammatory actions and lung disease	Histopathological, immunohistochemical analyzes
Manganyi et al., 2018	South African Journal of Botany	Investigating the biodiversity of isolated endophytic fungi	*P. sidoides*	-	Morphological and molecular techniques, antibacterial activities	*Escherichia coli (In vitro)*
Sun *et al.*, 2019	Biomedicine & Pharmacotherap	Use of phytochemicals to increase the anti-cancer effectiveness of cisplatin	*H. helix*	-	Anti-cancer of cisplatin	Head and neck cancer
Della Pasqua et al., 2019	J Ethnopharmacol.	Investigate anti-inflammatory activity of aqueous extract of the leaves	*M. glomerata*	Fresh leaves	Pharmacological Study and Anti-Inflammatory Activity	Rats, Ultra High Efficiency Liquid Chromatograpy (UHPLC/MS)
Samie *et al.*, 2019	J Ethnopharmacol.	To evaluate anti-cryptococcal and anti-pathogenic activity,	*P. sidoides*	Tubers (leaves and root)	Antifungal activity	*Cryptococcus neoformans*

Table 1. Bibliographic and experimental research on the use of medicinal plants in the treatment of respiratory diseases.

(-): Not informed by the review.

The *M. glomerata*, is popularly known as guaco and its extraction takes the form of essential oils, tinctures or aqueous extracts (Gasparetto et al., 2010). The plant contains coumarins, lactones, sesquiterpenes, diterpenes, phytosterols and flavonoids (Rufatto et al., 2012). The coumarins are responsible for anti-inflammatory, bronchodilator, antitussive and expectorant (Czelusniak et al., 2012), and can be used in respiratory diseases.

Rufatto et al. (2012) reported efficacy of *M. glomerata* in the treatment of fever, respiratory diseases and thus this herbal medicine can be used in a broad range of diseases. Their tests are based on use in humans and animals. When associated with other plants/substances does not lose its properties.

Tavares et al. (2006) evaluated Saratosse® syrup, which has composition of *M. glomerata*. The 15mL of syrup was used four times daily in each volunteer for 28 days as a result, the volunteers with flu-like symptoms and pharyngitis no longer had cough or nasal

discharge. Mello & Mello (2006) also tested the herbal medicine Fimatosan® with results comparable to the medicine Abrilar® based on H. helix.

Mangueira et al. (2013), reported the recognition of the *H. helix* extract etanolic, has been recommended in the treatment for asthma. In another study. Lang et al. (2015), reported efficacy of *H. helix* as antitussive, anti-inflammatory and antiviral agent and also against influenza A (Song et al., 2014; Song et al., 2015).

In addition to various uses already discussed, it is possible to include other studies that relate their applications to the active principles of the plant. Its effectiveness can be proven by the use of Abrilar®, which contains extract etanolic of the leaves of *H. helix*, and increases mucociliary and expectorant velocity, this is due to the presence of saponins in this plant (Mello & Mello, 2006).

Herbal Medicine EPs® 7630, contains extract from the roots of *P. sidoides*, and can be used in the treatment of bronchitis, respiratory disease infections and tuberculosis that are directly related to cough symptoms (Timmer et al., 2013). In *P. sidoides* the leaves and roots are used, but the largest number of publications only mention the use of roots (Moyo & Staden, 2014). The *P. sidoides* is used by indigenous tribes for the treatment of respiratory system diseases and gastrointestinal problems (Linhares et al., 2010).

The benefits can also be verified by the use of these plants in the production of industrialized products, such as: Fimatosan®, consisting of extract of leaves of *M. glomerata*, Abrilar® composed of extract of leaves of *H. helix* (Mello & Mello, 2006), and Ps® 7630 based on the root extract of *P. sidoides* (Agbabiaka et al., 2008; Michaelis et al., 2011).

For cough inhibition, the presence of active substances such as saponins, flavonoids and coumarins is required. According to Czelusniak et al. (2012), these substances have expectorant, broncodilador and antitussive action, efficient in combating respiratory diseases. In *M. glomerata*, for example, the younger the leaves, the higher the incidence of coumarins. Flavanoids are present in *P. sidoides* and *M. glomerata*. Phenolic compounds are present in both *H. helix* and *P. sidoides*.

A study by Song et al. (2014) reports that herbal medicines are more potent when used in combination. The association of *M. glomerata*, *M. piperita*, *E. globulus* and *C. multijuga* met its specifications well, as there were no subsequent complaints about the symptoms described before its administration, such as purulency and cough formation (Tavares et al., 2006). However, according to Mello & Mello (2006), it can be noted that Abrilar® has a more relevant expectorant effect, rapid mucociliary effect, when compared to fimatosan phytotherapeutics® formulated from *M. Glomerata*. Both showed a decrease in the frequency of cough in guinea pigs.

4 I CONCLUSION

Herbal remedies based on *M. glomerata*, *H. helix* and *P. sidoides*, act safely and effectively as antitussive and expectorant, offering the treatment or even cure of symptoms such as cough, inflammation and expectoration.

After reading and analyzing different articles concerning, it is evident that the phytotherapeutics such as Fimatosan®, Abrilar® and Kaloba® obtained from these plants are guaranteed by ANVISA, leading to increasing reliability index for remarkable activity, helping to reduce or eliminate secretion, and finally, in the restoration of health.

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