

Biological Activity, Chemical Composition and Botanical Aspects of *Ageratum fastigiatum* (Gardner.) R. M. King et H. Rob.

Atividade Biológica, Composição Química e Aspectos Botânicos de *Ageratum fastigiatum* (Gardner.) R. M. King et H. Rob.

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Abstract

Ageratum fastigiatum is a plant of the genus Asteraceae, a family that includes about thirty tropical plants. Studies about *A. fastigiatum* have increased mainly due to its pharmacological and ethnobotanical relevance, as well as studies that have demonstrated the anti-inflammatory effects of different extracts of such plant and their use in pest control and insecticide production. Such aspects are relevant due to the constant demand for new drugs and the need to corroborate its traditional use, however, the literature still lacks studies that gather the main findings about a plant with so much potential. Thus, this review aimed to present the botanical, ethnobotanical, phytochemical and pharmacological aspects of the plant in order to provide an overview about the plant's state-of-the-art and to contribute to future studies regarding *Ageratum fastigiatum*. Through this literature review, it was demonstrated that the botanical and identification aspects of *A. fastigiatum* are well defined and registered among researchers and that *A. fastigiatum* is a plant whose biological action has demonstrated great potential for both commercial and public health applications, which makes it extremely attractive. However, the number of studies was relatively small, which proves to be a plant still very little explored.

Keywords: Brazilian Cerrado. Ethnopharmacology. Herbal Medicine. Medicinal Plants.

Resumo

Ageratum fastigiatum é uma planta do gênero Asteraceae, família que reúne cerca de trinta plantas tropicais. Os estudos a respeito da *A. fastigiatum* têm aumentado principalmente devido à relevância farmacológica e etnobotânica bem como estudos que demonstraram efeitos anti-inflamatórios de diferentes extratos da planta e o uso destes no controle de pragas e produção de inseticidas. Tais aspectos são relevantes diante da demanda constante de novas drogas e da necessidade de corroborar com o uso tradicional da planta, contudo, a literatura ainda carece de um trabalho onde estejam reunidos os principais achados a respeito de uma planta com tanto potencial. Assim, esta revisão teve como objetivo apresentar os aspectos botânicos, etnobotânicos, fitoquímicos e farmacológicos da planta a fim de proporcionar um panorama sobre o estado da arte sobre a mesma e contribuir para estudos futuros a respeito da *Ageratum fastigiatum*. Por meio da presente revisão de literatura, foi demonstrado que os aspectos botânicos e de identificação da *A. fastigiatum* são bem definidos e registrados entre pesquisadores e que a *A. fastigiatum* é uma planta cuja ação biológica demonstrou grande potencial para aplicações tanto comerciais quanto de saúde pública, o que a torna extremamente atrativa. Contudo, a quantidade de estudos foi relativamente pequena o que demonstra ser uma planta ainda muito pouco explorada.

Palavras-chave: Cerrado Brasileiro. Etnofarmacologia. Fitoterapia. Medicina. Plantas Medicinais.

1 Introduction

The Asteraceae family includes a large group of plants found mainly in tropical regions and widely distributed in Brazilian Cerrado (BREMER; ANDERBERG, 1994). This family comprises about 25,000 species of plants, distributed in about 1400 genera (GURIB-FAKIM, 2006). *Ageratum* is an Asteraceae's plant genus that gathers about thirty tropical plants being the *Ageratum conyzoides* the most studied species due its chemical and biological features (OKUNADE, 2002). However, *Ageratum fastigiatum* (Gardner.) R. M. King et H. Rob. is another species that has been increasingly studied in botanical, ethnobotanical and pharmacological aspects (DE LIMA CAMPOS *et al.*, 2018; AVELAR-FREITAS *et al.*, 2018) due to its pharmacological potential.

Regarding its commercial aspect, in Brazil, it is estimated that 25% of the R\$ 8 billion raised by the pharmaceutical industry in the year of 1996, were originated from the plant-derived medicines (BRASIL, 2016) and the greatest advantage of *Ageratum fastigiatum* is that there are a lot of studies that describe the plant's biological activity. The Brazilian Medicinal and Herbal Plants Program aims to provide safe access and rational use of medicinal and herbal plants with the sustainable use of biodiversity (BRASIL, 2016). For this reason, obtaining information about Brazilian native species is relevant, including for the public health purposes and policies.

Such aspect is not a local phenomenon, it is reported worldwide the use of natural products for therapeutic purposes. For instance, in the USA about 18% of the

population uses natural products (including plant-based or botanical preparations) for treatment or prevention of diseases (CAESAR; CECH, 2019).

Therefore, this review aims to present relevant botanical, ethnobotanical, phytochemical and pharmacological aspects of *A. fastigiatum* in order to provide subsidies for further studies and also support future researches with this medicinal plant.

2 Material and Methods

The present review contemplates information about ecological, botanical, ethnobotanical and pharmacological aspects of *A. fastigiatum*. In addition to the descriptive

approach, interpretative particulars related to its morphology and ecology were also included. The search for studies published until January 2021 was performed without restriction to the year of publication, in the electronic databases: CAPES, SciELO, Science Direct, Pubmed and Google Scholar, using the descriptor and keyword “*Ageratum fastigiatum*”. After reading and analyzing titles and abstracts, the articles that fitted the proposed theme and written in English and Portuguese languages were included in the present review.

3 Results and Discussion

The results for the online search for articles are presented in Table 1.

Table 1 - Summary of the main aspects related to *Ageratum fastigiatum**

Morphology Embryology	Biological Activity	Chemical Composition	Ethnobotanical distribution	Reference	Database
			+	Almeida <i>et al.</i> , (2004)	Capes, Google Scholar
	+			Avelar-Freitas <i>et al.</i> , (2013)	Capes, Google Scholar, Scielo.
	+	+		Avelar-Freitas <i>et al.</i> , (2015)	Capes, Google Scholar, Scielo, Science Direct
		+		Bohlmann <i>et al.</i> , (1981)	Capes, Google Scholar
		+	+	Bohlmann <i>et al.</i> , (1982)	Capes, Google Scholar, Science Direct
		+		Bohlmann <i>et al.</i> , (1983)	Capes, Science Direct
	+	+		Borges <i>et al.</i> , (2018)	Capes, Google Scholar
			+	Brandão <i>et al.</i> , (2012)	Science Direct
	+	+	+	De Lima <i>et al.</i> , (2018)	Google Scholar
	+			Del-Vechio <i>et al.</i> , (2007)	Google Scholar
+				Del-Vechio-Vieira <i>et al.</i> , (2008)	Capes, Google Scholar, Science Direct
	+	+		Del-Vechio-Vieira <i>et al.</i> , (2009a)	Capes, Google Scholar, Science Direct
	+	+		Del-Vechio-Vieira <i>et al.</i> , (2009b)	Capes, Google Scholar
	+	+		Del-Vechio-Vieira (2016)	Capes, Google Scholar, Scielo, Pubmed
+			+	Franca <i>et al.</i> , (2015)	Google Scholar
		+		Gonçalves <i>et al.</i> , (2011)	Capes, Google Scholar, Sciel.
		+	+	Petacci <i>et al.</i> , (2012)	Google Scholar
	+	+		Souza <i>et al.</i> , (2019)	Google Scholar, Pubmed

Legend: + means that such aspect was presented and/or tested in the selected studies. * from the evaluated articles after exclusion criterion.

Source: Research data.

23 documents were found where thesis, dissertations and abstracts published in scientific events annals were excluded. Thus, a total of 18 articles published in scientific journals were evaluated and the chemical composition was the mostly reported (66.7%) aspect.

3.1 Morphological Description

A. fastigiatum is a 1.5 m tall bush with petiolated and alternated/fasciculate leaves, acute apex, serrated and glandular margins on both sides (Figure 1). The blooming contains subcellular, glandular and lanceolate parts of acute apices. The Lilac corolla blooms with glandular trichomes in lacustrums, and the root shows secondary growth in the branching zone with secretory structures. The stem has an unstratified epidermis, stomates, simple tectonic trichomes and glandular capitalized trichomes (DEL-VECHIO-VIEIRA *et al.*, 2008). The presence of these trichomes has also been observed in the species of *A. conyzoides* (TAVARES; GIL; VIANA, 2000). The stomatodes of *A. fastigiatum*, as well as of other Asteraceae, are of the anomocytic type. However, different from other plants of the mesophyll genus, the parenchyma may have folds, which may increase the cell surface. As discussed by Del-Vechio and collaborators, morphological and anatomical structures are important for the correct identification of *A. fastigiatum* and may also guide phytochemical and pharmacological studies (DEL-VECHIO-VIEIRA *et al.*, 2008). In the present literature search, only one article was found that presents embryological aspects of *A. fastigiatum*. Franca *et al.* (2015) collected flower buds, flowers, and fruits in various stages of development of *Ageratum fastigiatum* and the obtained slides reinforced the heterogeneity of the familiar embryology and showed, for the first time, the anther wall development of the monocotyledonous type for *Asteraceae*. (FRANCA *et al.*, 2015).

Figure 1 - *Ageratum fastigiatum* in its natural environment, Brazilian Cerrado (left). Details of morphological features (right)



Source: Author

3.2 Distribution

While *A. conyzoides* is found throughout America, scientific reports indicate that *A. fastigiatum* is only found in

Brazil (FRANCA *et al.*, 2015). A study indicated a geographical distribution of Eupatorieae species in South-eastern and Southern Brazilian mountain ranges and demonstrated the presence of *A. fastigiatum* in all the localities of Serra Mantiqueira, in southeastern Brazil (ALMEIDA; PRADO; LEWINSOHN, 2004). Such region includes cities of the state of Minas Gerais as São João Del Rei (DEL-VECHIO-VIEIRA *et al.*, 2008), Diamantina (PETACCI *et al.*, 2012), Rio Paranaíba (BOHLMANN *et al.*, DEL-VECHIO-VIEIRA *et al.*, 2008); OHLMANN *et al.*, 1982) and Uberlândia (FRANCA *et al.*, 2015). The central region of Brazil also reported the presence of such plant as in the state of Goiás, although the authors did not specify the city (BOHLMANN *et al.*, 1982).

3.3 Ethnobotany

Brandão *et al.* (2012) studied the list of native plants used by the Brazilian population reported by the French naturalist Saint-Hilaire, through the volumes of the field books deposited in the *Muséum National d'Histoire Naturelle* in Paris, France. In 1824, Saint-Hilaire the French naturalist had already published books about the Brazilian flora; however, some of his field books had not yet been studied. In the volume B1, which contains the records from the analysis in Rio de Janeiro and Minas Gerais states, information was recorded about *A. fastigiatum* with the original name, written by Saint-Hilaire, "matta pasto". Further information described was that "flowers are viscous with a strong smell, and not grazed by cattle". Today the plant is popularly known as "mata-pasto" as well (DEL-VECHIO-VIEIRA *et al.*, 2008), and specifically in the city of Diamantina it is also denominated "enxota" (GONÇALVES *et al.*, 2011). The plant is used by the local population for healing and for anti-inflammatory and antimicrobial purposes (DEL-VECHIO-VIEIRA *et al.*, 2008, 2000). Local healers prepare the extract from freshly chopped leaves and branches (with or without inflorescences), which are then subjected to maceration. Following filtration, the aqueous extract is applied topically to treat pain and inflammation (GONÇALVES *et al.*, 2011).

3.4 Chemical composition

In samples of *A. fastigiatum* collected in Goiás State, the following constituents were isolated: germacrene-D (sesquiterpene), nerolidol and coumarin derivatives (from the roots) and, in the aerial parts, taraxasterol, lupeol acetate triterpenes, cauran type diterpenes and sesquiterpene lactones (BOHLMANN *et al.*, 1983). These were the first published studies that reported the chemical constituents in *A. fastigiatum*. Gonçalves *et al.* (2011) chemically evaluated the leaves and inflorescences of *A. fastigiatum* collected in the city of Diamantina (state of Minas Gerais) and verified, by means of gas chromatography mass spectrometry (GC-MS), the presence of triterpenes and steroids. The essential oil of

leaves and inflorescences presented the main constituents, the monoterpenes α -pinene and limonene, and the sesquiterpene germacren. The coumarin ayapin was isolated from the ethanolic extract. Del-Vechio-Vieira *et al.* (2016) reported the presence of tannins, coumarins, terpenes, sterols, saponins and the presence of considerable amount of flavonoids and phenolics in the ethanol extract of *A. Fastigiatum*.

Del-Vechio-Vieira *et al.* (2009a) evaluated the essential oil of *A. fastigiatum* and observed three major components as sesquiterpenes germacrene-D (24.15%), α -humulene (11.15%) and β -cedrene (10.63%) (DEL-VECHIO-VIEIRA *et al.*, 2008). Further chemical identification of the essential oil of *A. fastigiatum* was performed by Avelar-Freitas *et al.* (2015) and Souza *et al.* (2019), who also described biological activities of the essential oil. It was observed the decrease of lymphocytes and neutrophils positives for tumor necrosis factor (TNF) and beta-integrin expression on human lymphocytes, respectively (AVELAR-FREITAS *et al.*, 2015; SOUZA *et al.*, 2019). The identified compounds in Avelar-freitas *et al.* (2015) were a total of nine from which five of them were monoterpenes: α -pinene, β -pinene, β -myrcene, d-limonene and β -ocimene; and four sesquiterpenes: α -copaene, 4,8- β -epoxy-caryophyllene, germacrene and bicyclogermacrene. α -pinene was the major monoterpene and germacrene the major sesquiterpene (AVELAR-FREITAS *et al.*, 2019).

3.5 Biological activity

Results were reported in the literature regarding the use of the plant as extracts and as active molecules from plant extracts. This can be attributed to a synergistic action of the extract components, although there is no study that investigated this aspect exclusively for *A. fastigiatum*. In fact, synergy and antagonism are notoriously difficult to study, particularly given that natural products chemistry research methodology is typically devoted to reducing complexity and identifying single active constituents for drug development. In a recent review (2019) it was stated that it is common that isolation efforts on a botanical extract fail because activity is lost upon fractionation (CAESAR; CECH, 2019). For such reasons, the identification of bioactive markers or molecules should not overlap studies with the use of plant extracts so both approaches were considered.

3.6 Pest control and insecticidal effect

In order to identify alternatives to pest control in corn plantations, Tavares *et al.* (2009) evaluated the toxicity of plant extracts from Asteraceae family plants to species such as *Spodoptera frugiperda* Smith and Abbott (Lepidoptera: Noctuidae), the main corn pest (CAESAR; CECH, 2019). From all the evaluated extracts of *A. fastigiatum*, the ethanolic one was evaluated for insecticidal potential. Such plant extract showed toxicity higher than 70% in *S. frugiperda* eggs. Borges *et al.* (2018) evaluated the potential of the essential oil

of *A. fastigiatum* leaves in the management of plant-parasitic nematode *Meloidogyne javanica*, however the results showed that the plant's essential oil does not control *M. javanica* in lettuce (BORGES *et al.*, 2018). Avelar-freitas *et al.* (2013) also evaluated the toxic effect of the *A. fastigiatum* ethanolic extract on *Rhodnius nasutus* (Stål 1859), the vector of Chagas disease. After 120 hours of treatment, the ethanolic extract of *A. fastigiatum* showed a mortality rate of 77%. Together these results demonstrated that compounds present in *A. fastigiatum* have potential for the development of products for pest and insecticide management (AVELAR-FREITAS *et al.*, 2013).

3.7 Pharmacological aspects

Del-Vechio-Vieira *et al.* (2007) demonstrated antimicrobial activity for the methanolic extract of *A. fastigiatum*, as well as its hexane and dichloromethane subfractions. The extract and its fractions were active against *Staphylococcus aureus*, *Streptococcus mutans*, *Staphylococcus typhosa*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*. In addition, it was demonstrated antinociceptive activity of the extract and its fractions in the test of abdominal writhings induced by acetic acid, performed in animal model. The essential oil from leaves of *A. fastigiatum* also showed antimicrobial activity, but for a smaller diversity of microorganisms, *Staphylococcus aureus*, *Streptococcus mutans*, *Staphylococcus typhosa* and *Escherichia coli* (DEL-VECHIO-VIEIRA *et al.*, 2009b). In another *in vivo* experiment Del-Vechio-Vieira *et al.* (2009a) evaluated the analgesic and anti-inflammatory activity of the essential oil of *A. fastigiatum*. To analyze the analgesic activity, the acetic acid induced writhing test and paw licking test induced by formalin were used, as well as the hot plate test. In all tests the essential oil of *A. fastigiatum* demonstrated analgesic activity (DEL-VECHIO-VIEIRA *et al.*, 2009). To evaluate the anti-inflammatory effect, carrageenan-induced paw edema test and pleurisy inhibition tests were performed. In these studies, a significant reduction of the paw volume and leukocyte migration was observed when the animals were orally treated with the plant's essential oil, thus suggesting analgesic and anti-inflammatory activity of *A. fastigiatum* (DEL-VECHIO-VIEIRA *et al.*, 2009, 2016).

However, the precise mechanism involved in the plant's anti-inflammatory property as well as the chemical components directly responsible for such activity, have not been investigated. Nevertheless, studies have already indicated the ability of ethanolic and ethyl acetate extracts from the aerial parts of *A. fastigiatum* to reduce the production of inflammatory cytokines at *in vitro* leukocyte culture (AVELAR-FREITAS *et al.*, 2013). Additionally, the essential oil from leaves of *A. fastigiatum* reduced beta-integrin (CD18) expression on human lymphocytes, suggesting a possible effect on lymphocytes migration (SOUZA *et al.*, 2019).

4 Conclusion

A. fastigiatum is an important species, with pharmacological and public health interests. The findings, so far, indicated anti-inflammatory effect from different extracts of the plant and as a pest control agent and insecticide. Such aspects are relevant to the constant demand for new drugs. Through this literature review it has been demonstrated that the identification and botanical parameters are well defined and *A. fastigiatum* is a plant whose biological action has potential for either biotechnological and public health applications although it still is a little explored plant.

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