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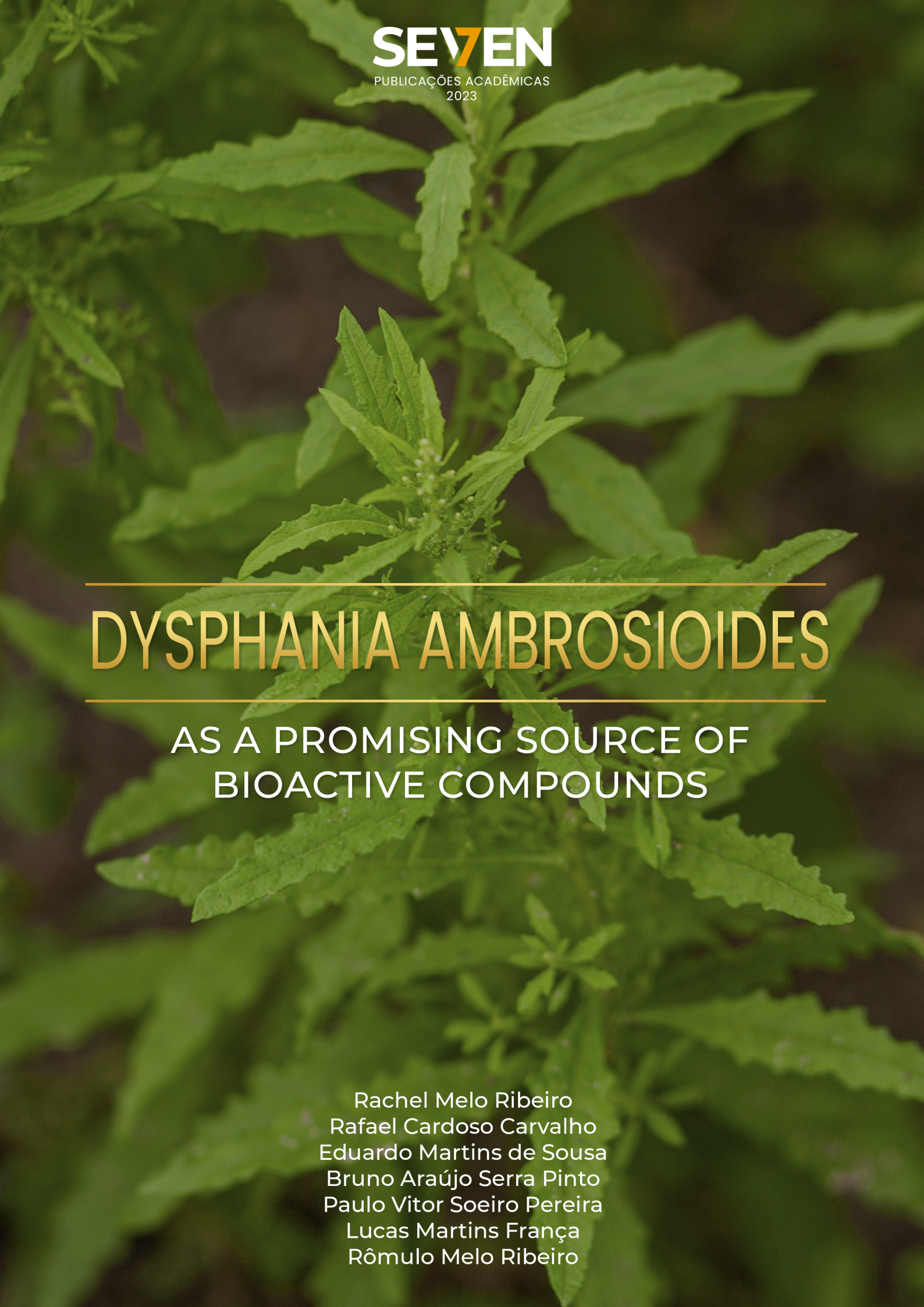

DYSPHANIA AMBROSIOIDES

AS A PROMISING SOURCE OF BIOACTIVE COMPOUNDS

Rachel Melo Ribeiro
Rafael Cardoso Carvalho
Eduardo Martins de Sousa
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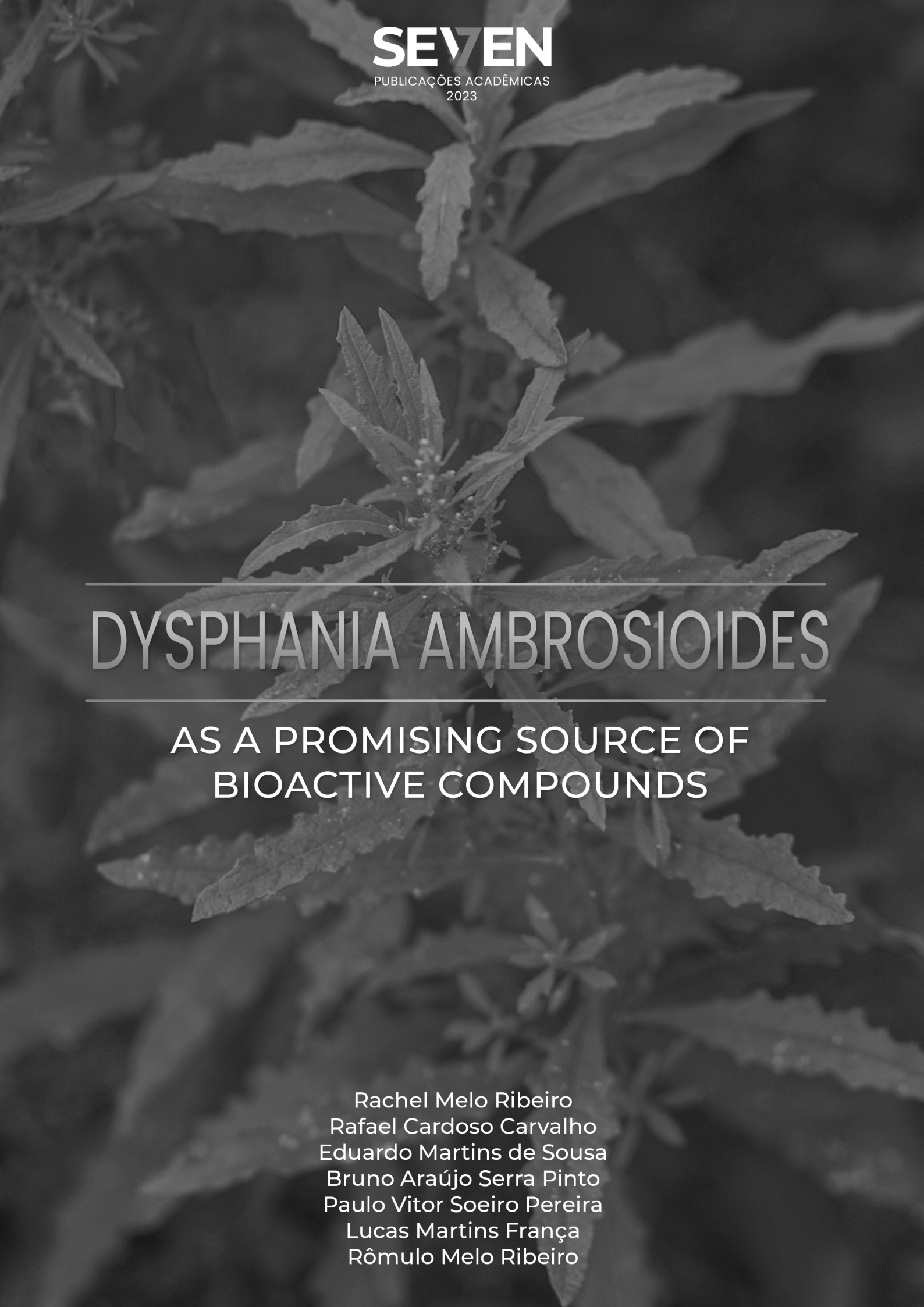

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PRESENTATION

Since antiquity, plants have been known for their medicinal properties, often used as an alternative or complement to conventional treatments. If you are interested in discovering more about the wonders that plants offer for human health, this book is essential reading for you. With detailed and up-to-date information, this practical guide is a valuable resource for anyone who wants to improve their health and well-being in a natural and holistic way.

This work is a fascinating journey into chemical *Dysphania ambrosioides* (L.) Mosyakin & Clemants (Amaranthaceae), popular as "mastruz" in Brazil, is a medicinal plant traditionally used in herbal medicines to treat diseases in various regions worldwide. The leaves of this plant are especially effective against pain, skin inflammations, kidney affections, coughs, tuberculosis, digestive and diaphoretic disorders, fracture, arterial hypertension, and cardiac diseases.

In this way, this book represents the opportunity to disseminate the plant species, serving as reference and consultation material for health professionals, professors, researchers, and academics, to provide updated information on phytochemical aspects and biological potential. developed with the objective of carrying out a review of research studies reported in the literature on mastruz, chemical aspects and biological potential, corroborating to increase the interest in scientific validation research of this plant.

The book consists of 6 Chapters, including introductory aspects, traditional use, chemical constituents, toxicity, pharmacological studies, and technological prospecting.

Finally, knowing that review works, whether systematic or integrative, are fundamental for the updating and performance of health professionals and the like, we wish you all an excellent reading, in the eagerness of this work to be able to strengthen the scientific literature with regard to the generation of knowledge in biological and health sciences, showing the relevance of scientific knowledge about medicinal plants, in addition to encouraging the dissemination of knowledge.

Dr. Rachel Melo Ribeiro

SUMMARY

General aspects regarding the relevance of *Dysphania ambrosioides* leaves

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1 INTRODUCTION

Dysphania ambrosioides (L.) Mosyakin & Clemants (synonym: Chenopodium ambrosioides L.), Amaranthaceae, it is considered one of the species most used among traditional treatments worldwide (LORENZI; MATOS, 2002). It is an aromatic herb popularly known as epazote, Santa-maria and mastruz, widely distributed throughout the world and recognized by their medicinal properties in human diseases.

This herbaceous plant, perennial or annual, was described in the Brazilian Pharmacopoeia 1st edition in 1926 (Pharmacopeia of the United States of Brazil, 1926), as an essential oil for the fight against intestinal parasites. In our country, D. ambrosioides occurs throughout the territory, being among the species most cultivated by the population. The scientific community over the years has shown many benefits from the extracts of the aerial parts (including flowers, leaves, and stem) of this plant species (BHAT; ADELOYE; ETEJERE; 1985; YADAV *et al*, 2007).

However, the leaves that specifically constitute one of the parts of the herb most used in different regions of the world has not been reported as a relevant component of the plant, though present products with chemical actives for the treatment of various diseases.

Different rural and urban communities in the Brazilian states use leaves mixed with milk to facilitate ingestion (LIMA *et al*, 2016). In 2009, the Federal Government of Brazil divulged a list of 71 plant species used in traditional medicine. The list denominated The National Register of Plants of Interest to the National Health System (RENISUS) presents D. ambrosioides occupies the 17th position (BRASIL, 2008).

In RENISUS, matruz leaves are indicated for the treatment of entoparasites, dermatitis, asthma, cough, and are also used as laxative, hepatoprotective and insecticide. To establish quality parameters for the plant species, Brazilian researchers performed a pharmacognostic study of D. ambrosioides.

In this work, the authors described the leaves as elongated, alternate, and petiolate with different sizes, identifying tectorial and glandular trichomes on both faces, presenting secretory cavities and idioblasts containing crystalline sand. Still, it was determined the presence of steroids in the main vein parenchyma (SÁ; SOARES; RANDAU, 2015). Several studies have reported the presence of different metabolic classes in D. ambrosioides leaves as a way of using them as markers of the plant species. Many of these compounds including flavonoids and terpenoids are associated with different medicinal properties in various plant species.

Thus, it is relevant to study the art of D. ambrosioides leaves as a promising source of bioactive compounds. This mapping provides a greater knowledge about active principles that indicate the potential scientific and technological development of mastruz to produce phytopharmaceuticals and phytotherapy's since there are already products that circulate commercially and that use it as raw material.

Like this, we can cite as example a compound of honey, mastruz, and Amapá milk produced by the Pronatus Amazonas® used for the treatment of cough and bronchitis. Other products that circulate are the massage creams associated with arnica and liquid soap, both produced by the company Suave Fragrance®.

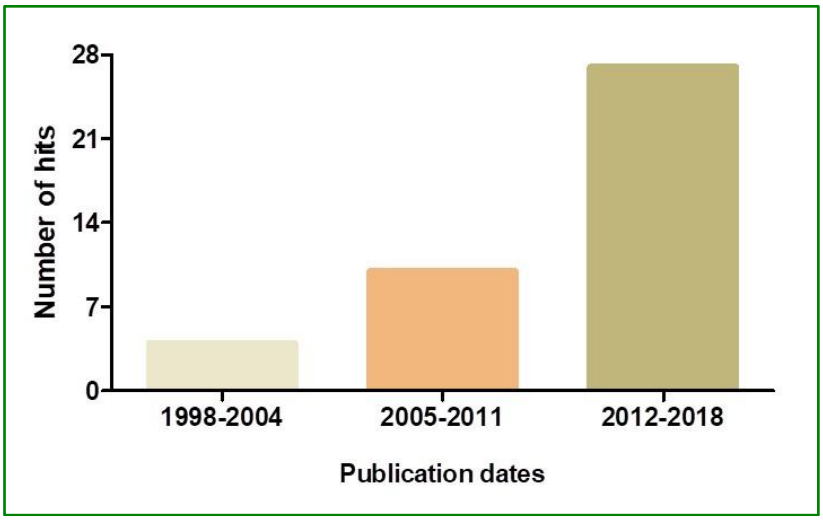
2 RELEVANCE

Several studies have described medicinal plants as a reservoir of biologically active compounds, in recent years. Recently, a review study has described the application of medicinal plants in the synthesis of biocompatible safe, and easy-to-acquire nanoparticles for wound healing (AYAZ; SUBHAN; SADIQ *et al*, 2017). Phytochemicals and their active substances are modulators of

different tissue pathways related to different pathophysiological processes, where monoterpenes are related to neuroprotection and cognitive ability, being useful in neurodegenerative diseases such as Alzheimer's (AYAZ; SADIQ; JUNAID *et al*, 2017). In addition, studies evidence that the catechins and diterpenes can transpose the mechanism of efflux-mediated drug resistance (OVAIS *et al*, 2018).

Thus, this review article gathered scientific evidence about chemical and pharmacological properties, and patents filed of the leaves of mastruz reported in the literature over the past 20 years. Keywords including D. ambrosioides and their synonyms were searched using electronic databases including ISI web of knowledge, Science Direct, Scopus, PubMed, Google Scholar, Google patents, and Espacenet (Figure 1).

Figure 1. Representation of the increase in the number of scientific publications on the biological potential of D. ambrosioides leaves from 1998 to 2018.



3 INFORMAÇÕES SOBRE *D. AMBROSIOIDES*

3.1 COMMON NAME

Dysphania ambrosioides is a species of eudicot with scientific synonyms *American wormseed*, *epazote*, and *Jerusalem-tea*.

Figure 2: Representative image of D. ambrosioides leaves. (Taxonomy, 2023)

Figure 3: Representative image of D. ambrosioides. (http://herbariovirtualbanyeres.blogspot.com/2010/05/chenopodium-ambrosioides-pazote-te-de.html).

3.2 TAXONOMY

Regarding the taxonomy of D. ambrosioides, have:

- **Kingdom:** Plantae
- **Division:** Magnoliophyta
- **Class:** Magnoliopsida
- **Order:** Caryophyllales
- **Family:** Amaranthacea
- **Gender:** Dysphania
- **Species:** Dysphania ambrosioides (L.) Mosyakin & Clemants

The homotypic synonym is *Chenopodium ambrosioides* L. Others synonyms included Ambrina ambrosioides (L.) Spach, Ambrina parvula Phil., Ambrina spathulata Moq., Atriplex ambrosioides (L.) Crantz, Blitum ambrosioides (L.) Beck, Botrys ambrosioides (L.) Nieuwl., Chenopodium integrifolium Vorosch., Chenopodium spathulatum Sieber ex Moq., Chenopodium suffruticosum subsp. remotum Vorosch., Chenopodium suffruticosum Willd., Orthosporum ambrosioides (L.) Kostel., Orthosporum suffruticosum Kostel., Teloxys ambrosioides (L.) W.A. Weber, Vulvaria ambrosioides (L.) Bubani.

Traditional uses of *Dysphania ambrosioides* leaves

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1 TRADICIONAL USES

Table 1 shows the indications reported by the population of different parts of the world and the use of *D. ambrosioides* leaves to treat the most variable diseases. In regions of low socioeconomic development, the use of *D. ambrosioides* becomes very relevant as a form of primary medical attention. The leaves, in the form of infusion and decoction, are the part of the herb most employed in the form of juice, poultice, and tincture.

The literature also shows that the oldest and most widespread traditional use of *D. ambrosioides* leaves in the world is as anthelmintics (MACDONALD, 2004). Additionally, in different regions, its use is broader and includes properties such as abortive, analgesic, laxative, antispasmodic, as well as for digestive beverages, tuberculosis, inflammation, colds, and flu, contuses and fractures, healing, dental diseases, hypertensive and cardiac diseases (Table 1). When used orally is generally added to cow's milk to facilitate ingestion. On the other hand, juice or milling is employed

topically in contusion and bone fractures (GOLENIOWSKI *et al*, 2006; RODRIGUES; ANDRADE, 2014), so that up to 5g/day of leaves are used for up to 3 days (GRISELDA; HORACIO; JORGE, 2016).

Table 1: Traditional use in various locations for *Dysphania ambrosioides* leaves

Country	Local name	Method	Tradicional use	References
Argentina	Quenopodio, Piako	Infusion	Analgesic, skin and kidney affections, antiviral, antireumatic, antispasmodic, stomach pain, anti-inflammatory,	Rondina; Bandoni; Coussio (2008)
		Decoction	anthelmintic, antiparasitic, hookworms, roundworms, and oxyrusvermicularis, ascarislumbricoides.	Griselda; Horacio; Jorge (2016)
		--	Digestive, stimulative, diaphoretic and antihelmintic	Goleniowski *et al*. (2006)
Bolivia	Caré	Infusion	Vermifuge, bruise, Abortion	Hajdu; Hohmann (2012)
Brazil	mastruz, mentruz, erva-de-Santa-Maria	Infusion	Inflammation, healing, constipation, flu	Pedino *et al*. (2016)
		Milling	Fracture	Rodrigues; Andrade, (2014)
		Infusion	Antihelmintic	Oliveira; Kffuri; Casali (2010)
		Juice	Bruises and wounds, fractures, urethral inflammation, ulcers, gastritis, rheumatism cancer and flu	Ribeiro *et al*. (2014); Roque; Rocha; Loiola (2010)
		Juice	Coughs, vermifuge	Albuquerque (2001)
		Cataplasm	Fractures, healing	Medeiros; Fonseca; Andreata (2004)
		---	Influenza, cough, bronchitis,	Albuquerque *et* al. (2007)
Dominican Republic	Sime, kontwá	Infusion	Vermifuge	Quinlan; Quinlan; Nolan (2015)
Ghana	-	Infusion; Decoction	Tuberculosis	Nguta *et al*. (2015)
Morocco	-	---	Hypertension, cardiac diseases	Eddouks *et al*. (2002)
		Infusion; Juice	Hypertension	Tahraoui *et al*. (2007)
		Infusion; Decoction	Cancer Fever, headaches, migraine, measles, syphilis	Kabbaj *et al*. (2012) Jamila; Mostafa (2014)
México	Paico, Mexican tea, American wormseed, goosefoot, epazote	Infusion	Abdominal pain, cough, flu, stomachache, antihelmintic	Quinlan; Quinlan; Nolan (2015); Juárez-Vázquez *et al*. (2013)

Nigeria	Kanunka uncono	Decoction	High blood pressure	LAWAL *et al.* (2009)
Republic of Zimbabwe	-	Aqueous Extract	Convulsions, nervous disorders	Vasisht; Kumar (2004)
Venezuela	-	Decoction	Antihelmintic	Carrillo-Rosario; Moreno (2006)
Tanzania	-	Decoction	Herpes simplex, cryptococcal meningitis	Kisangau *et al.* (2007)
United States of America	American Wormseed	-	Anodyne, Dysmenorrhea, Emmenagogueue, Lactogogue, Medicine, Narcotic, Nerve, Puerperium, Vermifuge	Hall (2005)

Source: Elaborated by the authors

Phytochemical constituents of *Dysphania ambrosioides* leaves

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1 PHYTOCHEMICAL CONSTITUENTS

Several studies of chemical characterization were able to isolate and identify different components in the leaves (Table 1). The richness of its chemical composition for different extracts obtained may, in part, explain the different uses of *D. ambrosioides*.

Table 1: Phytochemical compounds identified in leaves of *Dysphania ambrosioides*

Metabolite Class	Extraction		Analytical methods	Identified compounds	References
Flavonoids	-		-	Patuletin, Kaempferol	Song *et al.* (2014)
	Methanol-water		HPLC (reverse phase)	Myricetin, Quercetin, Rutin	Zohra *et al.* (2018)
	Ethanol 70% (crude extract)	Ethyl acetate fraction	HPLC–DAD	Quercetin	Jesus *et al.* (2018)
		Butanol fraction		Rutin	
		Chloroform fractions		Chrysin	
Cinnamamides	-		-	Methyldopamine	Song *et al.* (2014)
Phytosterol	Methanol		NMR spectroscopy	Stigmasterol	Shah; Khan, (2017)
	Methanol (crude extract)	ethyl acetate fraction		β-sitosterol Octadecanoic acid	
Coumarin		Dichloromethane fraction		Scopoletin	
Alkaloids		n-butanol sub fraction		Piperoylpiperidine	
Alkaloids	Essential oil		NMR spectroscopy	Piperoylpiperidine	Shah, Khan; (2017)
			GC-MS		Jardim *et al.* (2008)
			GC-MS and GC-FID		De Andrade Santiago *et al.* (2016)
Terpenes	Essential oil		GC-MS and GC-FID	α-terpinene, α-terpinenyl-acetate, beta-cymene, *p*-cymene, piperitone, carvyl acetate, piperitol acetate, trans-ascaridol, carvacrol, thymol, limonene,	Jardim *et al.* (2008); De Andrade Santiago *et al.* (2016); Kasali *et al.* (2006); Ávila-Blanco *et al.* (2014); Fdil *et al.* (2017); Jirovetz *et al.* (2000); Sá *et al.* (2014)
Furanoid lignans	-		-	Syringaresinol	Song *et al.* (2014)

Source: Elaborated by the authors

A qualitative analysis of secondary metabolites detected the presence of total phenolic, flavonoids, saponins and alkaloids in the aqueous (ARISAWA *et al*, 1971; PINHEIRO NETO *et al*, 2017) and methanolic extracts (ADEJUMO *et al*, 2011). Shah and Khan (SHAH; KHAN, 2017) suggest the presence of sitosterol, stigmasterol, octadecanoic acid, scopoletin and piperoylpiperidine at the leaf's methanol extract.

Recently, Zohra *et al*. (2018) identified others compounds such as rutin, myricetin, and quercetin. Monoterpenes are among the major constituents of the leaves being identified in the ethyl

acetate extract (KIUCHI *et al*, 2002), n-hexane-ethanol-methanol extract (AHMED, 2000), crude hexane extract (JARDIM *et al*, 2008) and in essential oil (SOARES *et al*, 2017).

Studies have been characterizing the main components of the essential oil of the leaves of *D. ambrosioides* that has shown differences between its major components depending on the region of collection. The essential oil of the leaves collected in India presented a high concentration of α-terpinene (65.4%) and ρ-cymene (29.4%), and a very low concentration of ascaridole (0.7%), limonene (0.2%) and α-terpinyl acetate (0.1%) (JIROVETZ *et al*, 2000).

Sá *et al*. (2014) performed the phytochemical characterization of essential oil extracted from the leaves of *D. ambrosioides* collected in state of Pernambuco, Brazil, and detected as main components α-terpinene (42.14%), α-terpinenyl acetate (31.57%), thymol (7.90%), and carvacrol (4.3%), with ρ-cymene and ascaridole being found in percentages 7.3% and 0.9%, respectively.

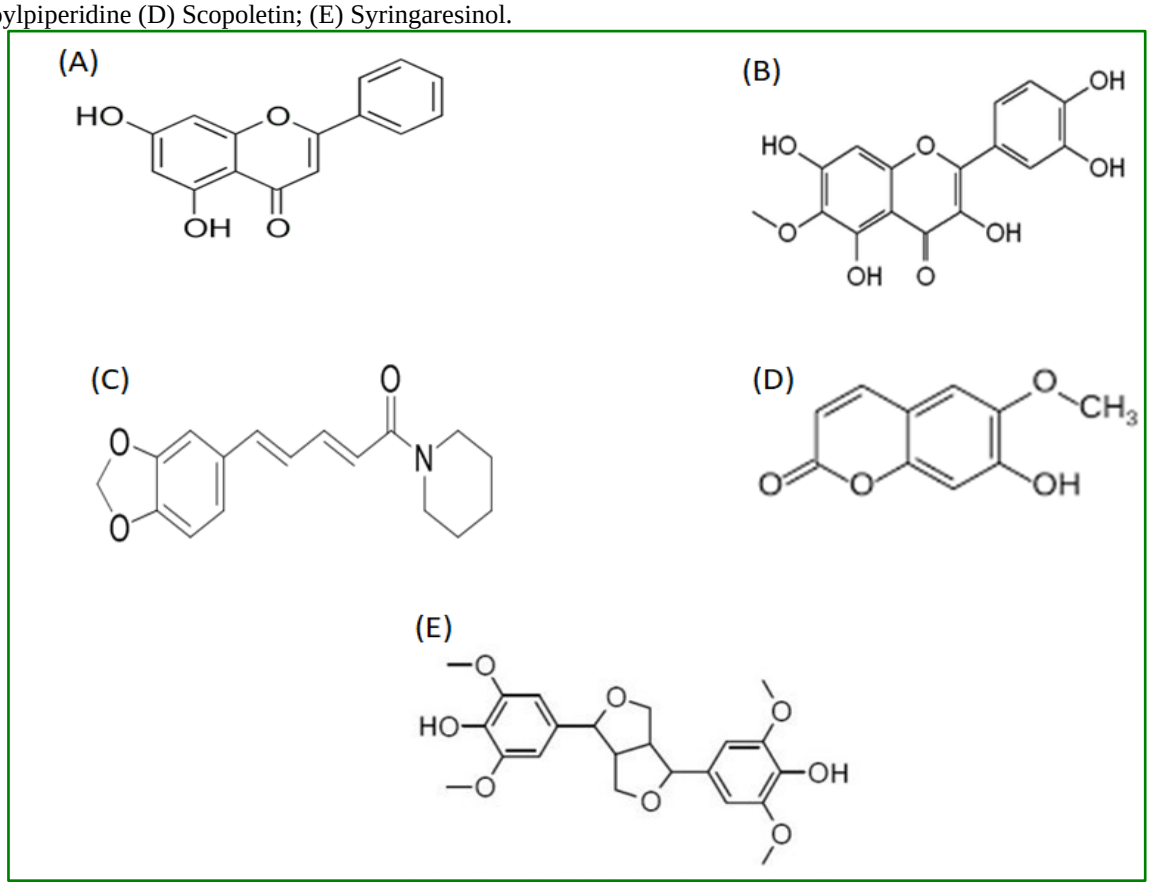
Additionally, studies performed by De Andrade Santiago *et al*. (2016) with essential oil extracted from leaves collected in the state of Minas Gerais - Brazil, determined that the main components found were α-terpinene (40.7%), p-cymene (21.8%) and trans-ascaridole (12.5%), and that piperitone epoxide and limonene compounds were found in lower percentages of 0.3% and 0.2%, respectively.

Other chemical exploration work of the sheets held by Fdil *et al*. (2017) identified p-cymene (41.7%), α-terpinene (34.8%), ascaridole (10.8%), thymol (3.5%) and carvacrol (1.6%) as major constituents of the herb collected in Morocco.

These variables may include seasonality and plant maturity, geographical origin, genetic variation, the stages of growth, the plant part used to produce the extract, and the drying and post-harvest storage (ANWAR *et al*, 2009).

Thus, all these compounds identified by different analytical methods for the plant species serve to control the quality of the leaves. The terpenes previously considered the main components responsible by the various biological effects of *D. ambrosioides*, are considered the main components of *D. ambrosioides* leaves with important pharmacological action and like products as flavonoids, coumarins, alkaloids, phytosteroids, cinnamamides, and furanoid lignans constantly reported in the literature in different signal transduction pathway components in several pathophysiological processes. Figures 1 compiled the chemical structure of these compounds.

Figure 1. The structure of different compounds in *D. ambrosioides* leaves. (A) Chrysin; (B) Patuletin; (C) Piperoylpiperidine (D) Scopoletin; (E) Syringaresinol.



Source: Elaborated by the authors

Possible biological properties and toxicity of *Dysphania ambrosioides* based on its chemical constituents

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1 STRUCTURE-ACTIVITY RELATION OF DIFFERENT COMPOUNDS IN *D. AMBROSIOIDES*

Table 1 compiled the chemical structure of these compounds and their pharmacological activities already described. The structure-activity relationship of these compounds contributes to the understanding of the mechanisms of action of this medicinal herb in several experimental models of pharmacological investigation that will be reported in this book.

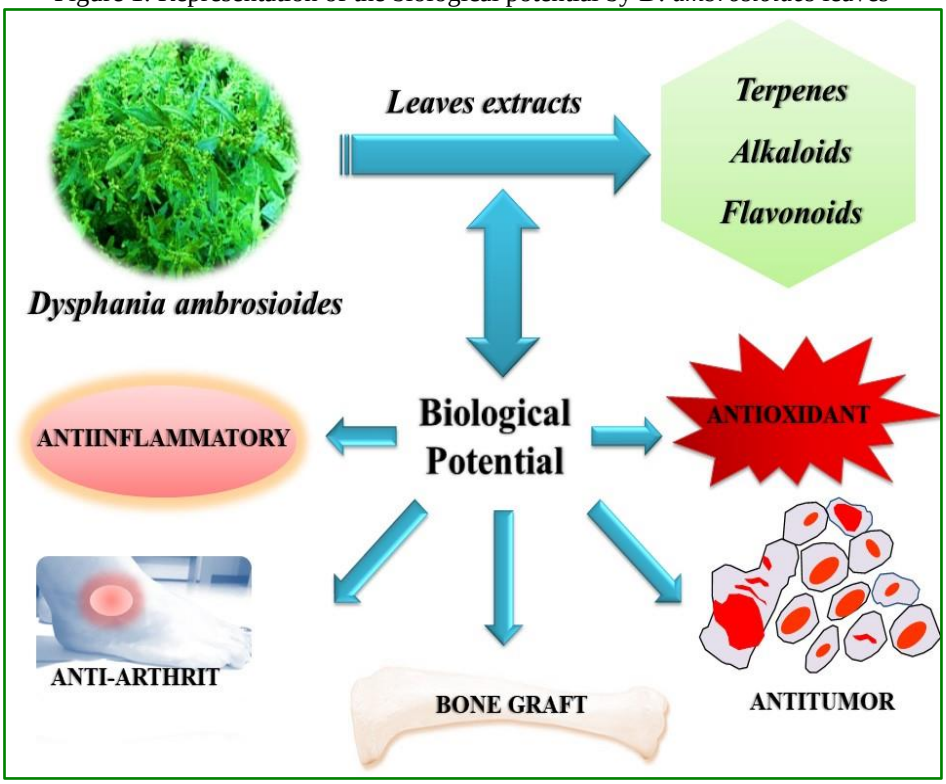
Table 1: The structure-activity relation of different compounds in D. ambrosioides leaves.

Chemical constituents	Biological Potential	Proposed mechanism	References
Chrysin	Antinociceptive Antiinflamatory	Inhibitor of COX2	Rauf *et al*. (2015)
	Gastroprotective	Angiogenesis (VEGF and basic fibroblast growth factor) and PPAR –y agonist	George *et al*. (2015)
	Anticancer	Inhibitor of aromatase Antiangiogênese	Lephart (2015) Rani *et al*. (2015)
	Antidiabetic	PPAR-y agonist	Rani *et al*. (2016)
Patuletin	Antinociceptive	Activation of the L-arginine/NO/cGMP/KATP pathway Modulation of glutamatergic systems	Zarei *et al*. (2018)
	Anticancer	Indutor de apoptose / inhibitor of fatty acid synthase	Zhu *et al*. (2017)
	Antioxidant	Increase in glutathione peroxidase and superoxide dismutase	Abdel-Wahhab *et al*. (2005)
Piperoylpiperidine	Antiinflamatory	Decrease of interleukin 1β and interferon	Gorgoni *et al*. (2017)
	Anticancer	Antioxidant Chemoprevention by G2/M phase cell cycle arrest through	Rhater; Madhulika (2018)
	Antidepressant	Regulation of serotonergic and dopaminergic systems	Khom *et al*. (2013)
Scopoletin	Antidiabetic	PPAR-y agonist Akt phosphorylation GLUT2 translocation Anti-glycation	Chang *et al*. (2015)

Source: Elaborated by the authors

In the last decade, preclinical tests have increased substantially to prove pharmacological activity for leaves, which have demonstrated a high biological potential to serve as a source of raw material for the manufacture of herbal products in the treatment of various diseases (Figure 1).

Figure 1: Representation of the biological potential by *D. ambrosioides* leaves



Source: Elaborated by the authors

2 TOXICITY

Pereira *et al*. (2010), evaluated the hydroalcoholic extract of *D. ambrosioides* leaves in sub chronic toxicity tests in mice. The animals received the extract daily at the doses of 5, 50 and 500 mg/kg by gavage for 15 days. The evaluation of the animals at the end of treatment revealed an increase in the number lymph node cells among animals that received the higher dose of 500 mg/kg.

The number of cells in the bone marrow was higher in treated animals, which also showed a lower number of peritoneal cells. There were no differences in hepatic transaminases levels, but there were significant reductions in the levels of albumin, triglycerides, and VLDL at the highest doses. In this study, it was not observed death of the animals during the protocol. Thus, the authors suggest that the treatment promotes punctual changes and that D. ambrosioides leaves extract is safe in adequate doses.

Subsequently, da Silva *et al*. (2014) evaluated the acute and sub chronic toxicity of the aqueous extract in rats. In the acute test, the dose of 3.0 g/kg elevated the serum levels of hepatic transaminases. In the sub chronic studies, the extract used in the dose of 1.0 g/kg for 15 days increased the serum levels of creatinine and alanine transaminase. Histopathological analysis of liver tissue of this same study showed mild vacuolization in the hepatocytes of the animals. The results suggest that oral administration of D. ambrosioides leaves promotes mild hepatic and renal changes in rats. The authors state that these low levels of toxicity may not be significant in healthy individuals but may to accentuate pre-existing disorders on liver and kidney.

Thus, as reported in previous study the consumption of the leaves is not presenting toxic risks related to ingestion of *D. ambrosioides* (POTAWALE; LUNIYA; MANTRI; MEHTA *et al*, 2008). In contrast, more testing is needed to discard complications associated to intoxication.

The leaf's methanol extract was evaluated in male Sprague Dawley rats by gavage, during 28 days of treatment. The animals received different doses of the extract and at the end of the treatment had their reproductive parameters evaluated. The results showed that the *D. ambrosioides* leaves reduce motility, viability as well as fertility of spermatozoa. In this study, there was observed still decrease in the plasma testosterone, follicle stimulating hormone and luteinizing hormone in a dose-dependent manner. The highest dose (150 mg/kg) promoted oxidative stress in the reproductive organs. These results suggest a reversible suppression of spermatogenesis after use of methanolic extract (AIN *et al*, 2018).

Dysphania ambrosioides: Pharmacological potential in human diseases

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1 PHARMACOLOGICAL STUDIES FOR *D. AMBROSIOIDES* LEAVES

1.1 ANTI-INFLAMMATORY AND ANALGESIC

Cruz *et al*. (2007) evaluated the anti-inflammatory potential of the hydroalcoholic extract in preclinical tests. The extract at the dose of 5.0 mg/kg/i.p. was compared to concanavalin A at the dose of 0.05 mg/kg (a substance capable of inducing activation of macrophages and cell proliferation), both the products were used in the treatment of C3H/HePas mice, also evaluating the *in vitro* activity of macrophages. The authors evaluated the effect of the extract on lymphoid organs cellularity. The results indicated macrophage spreading and phagocytic ability and induced a significant increase in spontaneous NO production. The authors demonstrated that the extract induced the macrophage activation and increased cell recruitment/proliferation in secondary lymphoid organs.

The analgesic potential of the leaves of *D. ambrosioides* was demonstrated in an experimental model of algesia by acetic acid (IBIRONKE; AJIBOYE, 2007. SOUSA *et al*, 2012). Trivellatograssi

et al. (2013) corroborate these findings, the authors used the ethanolic extract of leaves and stems at doses of 150-500 mg/kg/gavage to evaluate anti-nociceptive activity, prostaglandin E2 (PGE2; nmol), capsaicin (PAC, 1.6 μg) and bradykinin (BK, 10 nmol) in animal model of formalin-induced hyperalgesia (2.5%). The extract at the highest dose reduced formalin-induced nociception in both phases of the pain (neurogenic and inflammatory) with maximal inhibition of 95.6%, as well as inhibited PGE2, PAC, and BK-induced nociception in 68%, 53%, and 32% respectively. Chemical analysis performed in this study identified rutin, quercetin, and chrysin presents in the hydroalcoholic extract (JESUS *et al*, 2018). The presence of these compounds might partially explain the anti-inflammatory and analgesic mechanism of *D. ambrosioides*, once chrysin has antioxidant, anti-allergic and anti-inflammatory activity with a significant effect in PGE2 and Thromboxane A2 production (JESUS *et al*, 2018).

Hydroalcoholic extract and the hexane fraction were studied in animal sepsis model induced with cecal ligation and puncture (RIOS *et al*, 2017). The authors demonstrated that the extract and its fraction induce a modulatory effect on immune system of the animals, observing greater activation of mononuclear phagocytes and reduction in the levels of pro-inflammatory cytokines. In this study, the extract and the hexane fraction increased the NO production. In this study, *D. ambrosioides* also promoted the bacterial growth control in animals.

1.2 ANTI-ARTHRITIC

The hydroalcoholic extract was evaluated in osteoarthritis model in rats by intra-articular injection of sodium monoiodoacetate (CALADO *et al*, 2015). The extract 5 mg/kg and 50 mg/kg showed to reduce cell infiltration in the cartilage and synovium, so that the animals presented lower intensity of allodynia and hyperalgesia. Molecular docking was performed to evaluate the compatibility of ascaridole, one of the main constituents present in the extract, with the glutamate receptor N-methyl-D-aspartate (NMDA) once this receptor is involved in the control on inflammation and pain in osteoarthritis. Regarding molecular coupling, ascaridole showed an affinity by the NMDA receptor binding. The authors suggest that the anti-arthritic effect of *D. ambrosioides* leaves may be related to the antagonistic effect of ascaridole on the NMDA receptor.

The anti-arthritic potential of mastruz was recently characterized in rheumatoid arthritis model by collagen in DBA1/J mice. After 21 days of induction, the animals received the extract (5 mg/ kg) or methotrexate, used as the standard drug. After analyzing the serum levels of pro-inflammatory cytokines in addition to antioxidant enzyme activity, bone density, and histopathological analysis, the authors suggest an anti-arthritic action for *D. ambrosioides*. The extract showed a significant reduction in the neutrophilic and macrophage percentages, with animals presenting proliferation of

fibroblasts and synovial hyperplasia, indicating their direct participation in the inflammatory process in rheumatoid arthritis (PEREIRA *et al*, 2018).

1.3 ANTIMICROBIAL STUDIES

Jesus *et al*. (2018) found that *D. ambrosioides* are promising for antimicrobial therapy. The extract and all apolar and polar fractions were active against important microorganisms. However, the ethyl acetate fraction was shown to be the most promising with inhibition of many infectious agents. Mabona *et al*. (2013) evaluated the antimicrobial activity of *D. ambrosioides* leaves against methicillin-resistant *Staphylococcus aureus* and gentamycin-methicillin-resistant *Staphylococcus aureus* strains. According to the minimum inhibitory concentration (MIC) values obtained for the aqueous and dichloromethane extracts: methanol obtained for the study; the authors segmented broad-spectrum antimicrobial efficacy for the organic extract.

Limaverde *et al*. (2017) studied the antibiotic action of the essential oil obtained from the leaves of mastruz and its α-terpinene constituent, verifying that these do not present clinically relevant antibiotic action against *Staphylococcus aureus* IS-58. However, this study also evaluated the essential oil and its terpene when associated with tetracycline and ethidium bromide to evaluate the synergistic properties of these drugs. The essential oil reduced the MIC of the antibiotics tetracycline and ethidium bromide (EtBr) by to reduce the efflux pump activity of this multiresistant strain.

A similar study was recently developed by de Moraes *et al*. (2018) for the essential oil and α-terpene. In this work, efflux pump inhibition was tested using sub-inhibitory concentrations (¼ MIC) of α-Terpinene and the essential oil from *D. ambrosioides* leaves, aiming to evaluate the capacity of both in the decreasing of EtBr and norfloxacin MIC, substrates for the efflux pump coded for the norA gene, present in *S. aureus* 1199B and 1199 (wild-type) strains. Though the essential oil has been able to inhibit the pump, the α-terpinene alone had no clinically relevant antibacterial action and was unable to reduce the MIC of antibiotics despite being the main constituent present in the oil in this study. Therefore, the authors suggest that inhibition of the pump may be related to the other components present in the oil at low concentrations.

In gastric disorders, *D. ambrosioides* leaves were evaluated against Helicobacter pylori. Liu *et al*. (2013) evaluated an oral formulation containing *D. ambrosioides* leaves (0.64 mg/ml) against *H. pylori*-resistant strains. The authors evidence that the herb medicinal was able to inhibit the bacteria in a period of 4h after incubation.

Posteriorly, Ye *et al*. (2015) evaluated the effect of *D. ambrosioides* against *H. pylori*-infected mice compared to triple therapy (lansoprazole, metronidazole, and clarithromycin) using urease test and histological analysis. The results showed that the effect antimicrobial on animals treated with *D.*

ambrosioides and triple therapy were not statistically different. Histopathological analysis of the gastric mucosa showed that the animals treated with the herb and those treated with the triple therapy did not present inflammation or pathological alterations.

The properties of hydroalcoholic crude extract (HCE) from the leaves of *D. ambrosioides* was evaluated on the murine infection with *Leishmania amazonensis* in a study performed by Patrício *et al*. (2008). Treatment consisted of administering 5.0 mg/kg/day of THC by gavage or intralesional injections of the extract at 4-day intervals, both experiments were performed by a period of 15 days and meglumine antimoniate was used as a positive control. The study demonstrated that the administration of *D. ambrosioides* on the lesion promoted positive effect in controlling the spread of the infection, so the authors suggest that there is an increase in the production of nitric oxide responsible for this effect. Previous study by Pastor *et al*. (2015) developed in vivo in BALB / c mice infected with *Leishmania amazonensis* promastigotes evidence that the presence of the ascaridole and carvacrol compounds present potential use for antileishmanial therapy.

In the search of new therapeutic alternatives for the treatment of malaria, Cysne *et al*. (2016) evaluated *in vitro* and *in vivo* studies the antiplasmodial potential of HCE. Initially, the authors verified the molecular affinity of the HCE in relation to total proteins of the erythrocytes infected with *Plasmodium falciparum* through surface plasmon resonance and its plasmodicidal potential assessed in a *P. falciparum* culture. In this study, BALB/c mice infected with *Plasmodium berghei* were treated intraperitoneally with chloroquine (45 mg/kg) or HCE (5 mg/kg), observing the survival rate and parasitemia of the groups evaluated. The results demonstrated that HCE present higher binding affinities to the total proteins of erythrocytes infected and inhibit parasite growth (IC50 25.4 g/ml). Treatment with HCE increased survival and decreased parasitemia in infected animals suggesting that *D. ambrosiodes* presents compounds with potential use for antimalarial therapy.

Oral administration of the essential oil of *D. ambrosioides* leaves (10-100 mg/kg) showed a positive effect related to antimicrobial activity against *Entamoeba histolytica* by dose-dependent manner. The antiprotozoal activity was attributed to the ascaridole, substance present in essential oil used in this study (ÁVILA-BLANCO *et al*, 2014). In addition, Neiva *et al*. (2014) demonstrated that the leaves have important activity against *Giardia lamblia*.

1.4 DERMATOLOGICAL DISEASES

The essential oil obtained from the leaves showed an antifungal effect against *Aspergillus flavus*, *Aspergillus glaucus*, *Aspergillus niger*, *Aspergillus ochraceous*, *Fusarium oxysporum*, and *Fusarium semitectum* at concentrations of 0.05%, 0.1%, and 0.3%, respectively. The main fungitoxic component of this study was ascaridole (JARDIM *et al*, 2008). Mabona *et al*. (2013) evaluated the

antifungal activity for dichloromethane - methanol extract of *D. ambrosioides* leaves against *Trichophyton mentagrophytes*. In this study was observed significant results with an antifungal potential of the product tested.

1.5 ANTIOXIDANT

Antioxidant activity of methanolic extract aqueous (80%) of *D. ambrosioides* leaves was assessed using in vitro assays by 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity, superoxide anion scavenging activity, and Iron chelating activity. However, no significant result was observed for this activity (ABOUZID *et al*, 2008).

De Andrade Santiago *et al*. (2016) measured in vitro the antioxidant activity of essential oil extracted from leaves of *D. ambrosioides* by the β-carotene-linoleic acid and DPPH assays. The lowest and highest antioxidant activities observed in the p-carotene-linoleic acid system were 25 and 500 mg/mL, respectively. The concentrations of 300 and 500 μg/mL showed low antioxidant activity and no presented significant difference. This finding was attributed, according to the authors, to the predominance of monoterpenes hydrocarbons present in the oil composition, which in turn, show low solubility on the medium reaction of $DPPH^{\bullet}$ assay once this test uses methanol or ethanol as solvent.

On the other hand, Pinheiro Neto *et al*. (2017) evaluated the antioxidant potential by $DPPH^{\bullet}$ assay from the aqueous extract of the leaves, which evidenced a significant antioxidant activity. In this study, the antioxidant potential of the leaves was related to the majority presence of the oxygenated monoterpenoids that could be acting synergistically (FDIL *et al*, 2017).

1.6 ANTITUMOR

Ruffa *et al*. (2002) evaluated the activity of the methanolic extract in a human hepatocellular carcinoma cell line (Hep G2). In this study, the authors evidenced that there was no suppression of tumor growth. Subsequently, the anti-tumor activity was evaluated by Nascimento *et al*. (2006), who studied HCE (5 mg/kg / i.p.) on Ehrlich tumor development in mice. The tumor cells were implanted on the left footpad (solid tumor) or in the peritoneal cavity (ascitic tumor). The HCE reduced both tumor forms and increased survival of tumor-bearing animals. The authors suggested a potent antitumor effect.

In studies developed by Cruz *et al*. (2007), with inoculation of hydroalcoholic extract of leaves of *D. ambrosioides* via intraperitoneal in rats, it was evidenced that there was no increase in the number of cells in the bone marrow, nevertheless was observed an increase in the number of cells on peritoneal cavity and lymphoid organs (spleen and lymph nodes). The high activity of macrophages

increased the production of nitric oxide and cellular recruitment to the secondary lymphoid organs, which may explain the antitumor activity of *D. ambrosioides.*

Sowemimo *et al*. (2007) found that *D. ambrosioides* leaves contain bioactive compounds against telomerase activity. Additionally, the authors verified that this effect was not accompanied by mutagenesis, suggesting a selective cytotoxic activity for the leaves.

Tauchen *et al*. (2018) evidenced the potential antioxidant and anti-proliferative effect on a broad spectrum of cancer cells. Antioxidant potential was demonstrated by DPPH●, while cytotoxic activity (MTT assay) was analyzed in different cell lines (Caco-2, Hf-29, and Hep G2), suggesting that the extract of *D. ambrosioides* might serve as a prospective material for further development of novel plant-based antioxidant and/or anti-proliferative agents

1.7 HYPOTENSIVE

The hypotensive properties were evaluated in normotensive anesthetized rats with sodium pentobarbital 50 mg/kg. After a 30 min stabilization period, baseline blood pressure and the heart rate (HR) were recorded. The study involved AE, methanolic fraction (MF), ethyl acetate fraction (AcF), and aqueous Soxhlet fractions (AqF), administered intravenously in different doses. The interval among injections was usually 10 minutes after all blood pressure parameters had returned to control values. In the second experiment, after the stabilization period, a bolus injection of N(ω)-nitro-L-arginine methyl ester (L-NAME; 20 mg/kg) or Atropine (1 mg/kg) was performed, and after 30 min was performed the administration of the extract or fractions (5 mg/kg). Differences in systolic blood pressure and HR induced by MF and AcF were compared before (control) and after L-NAME or Atropine administration (ASSAIDI *et al*, 2014).

The results indicated clearly that the AE promoted hypotension in a dose-dependent manner accompanied by a bradycardic effect in the highest dose. Interestingly, MF and AqF promoted blood pressure reduction without heart rate change. The hypotensive effect of *D. ambrosioides* leaves was considerably attenuated in the presence of Atropine and remains unchanged in the presence of L-NAME, probably because of stimulation of the type 2 muscarinic receptor present in the heart, and not necessarily due to its vasodilator effect in relation to the muscarinic receptor located at the vascular level. Thus, the authors suggested that the hypotensive effect may be partially associated with their cardiac effects (ASSAIDI *et al*, 2014).

1.8 WOUND HEALING AND BONE METABOLISM

The aqueous extract from leaves of *D. ambrosioides* showed its potential use in treatment cutaneous wounds, evidenced by the higher concentration of fibroblasts at the focus of the wound

(SÉRVIO *et al*, 2011). Other study evaluated the effect of topical application of leaves ethanolic extract, showing a significant reduction in wound area, absence of bleeding and secretions purulent, as well as elevation of inflammatory mediators (TRIVELLATOGRASSI *et al*, 2013).

The pharmacological potential on bone metabolism to *D. ambrosioides* has been reported in the literature with the validation of a herbal product on bone regeneration (PINHEIRO *et al*, 2013). Preliminary studies conducted by our group showed that the cataplasm prepared from fresh leaves has potential for repair of soft tissue defects and bone fractures induced experimentally in rabbits.

The results were based on evaluation of the inflammatory process, edema inhibition, and radiographic analysis (PINHEIRO *et al*, 2005). Subsequently, also we evaluated in rabbits, the effect of the cataplasm of *D. ambrosioides* leaves on bone fractures, showing that the product is biocompatible since there were no changes in adjacent tissue or allergic reactions, besides promoting osteogenesis (PINHEIRO *et al*, 2015).

Recently, we have demonstrated the potential of the bone graft of *D. ambrosioides* applied in gel form as strategies for improved osseointegration and osteoinduction on femur fractures induced in rabbits, using analysis biomechanics, as well as radiographs, histopathological analysis, and immunostaining for data evaluation. In this study, we show the biocompatibility and therapeutic efficacy of the product tested in the treatment of bone fractures (PINHEIRO *et al*, 2017).

The repair capacity of bone tissue and bone neoformation were evaluated after use of a hemostatic sponge biomaterial impregnated with the aqueous extract of mastruz in an experimental model of tibial fractures induced in rats. The biomaterial showed high regenerative capacity with a larger quantity of endosteal and periosteal bone formation, so demonstrating the potential for bone neoformation (PENHA *et al*, 2017).

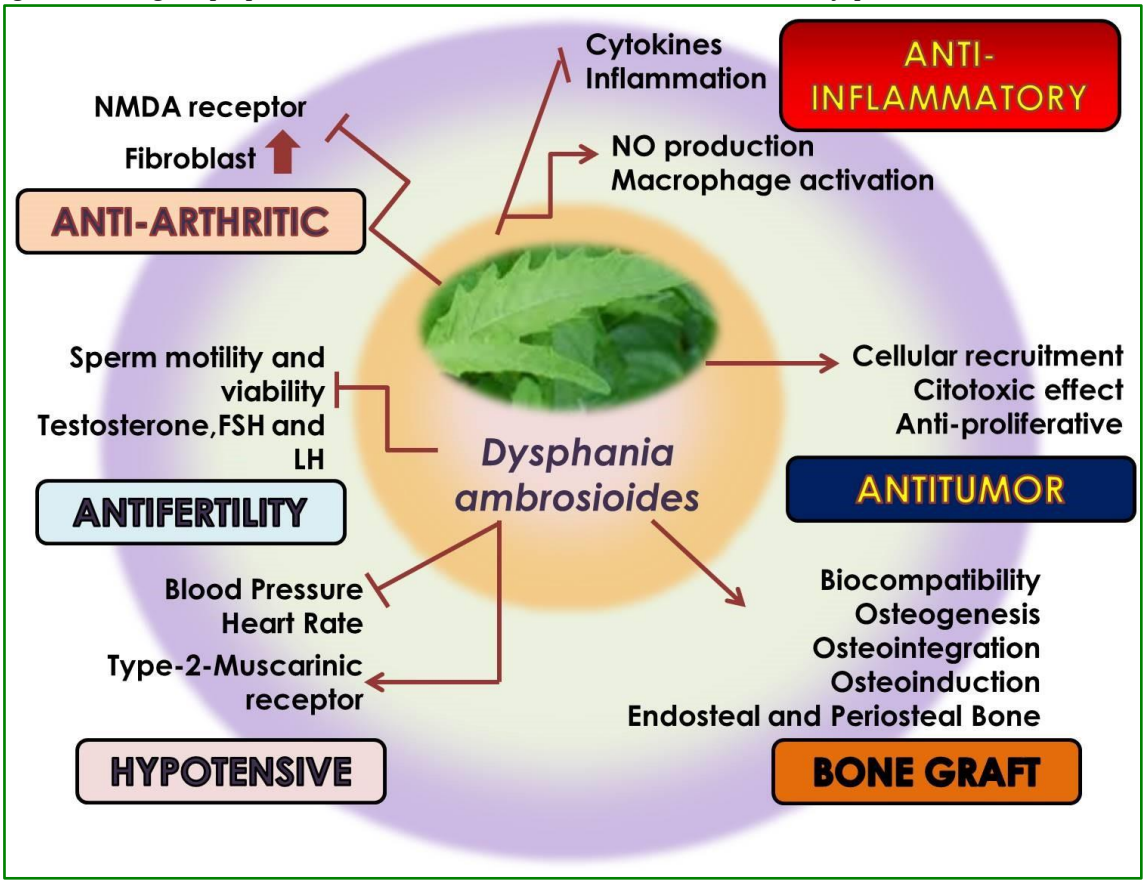
The efficacy of *D. ambrosioides* leave on bone metabolism was evaluated in the use of the hydroalcoholic extract in a model of osteoporosis ovariectomy-induced in rats. In this study, the herb prevented bone loss in animals contributing to the scientific validation of *D. ambrosioides* on bone regeneration (SOARES *et al*, 2015).

1.9 PROPOSED MECHANISM OF ACTION FOR D. AMBROSIOIDES LEAVES

Figure 1 shows different secondary metabolites that confer important pharmacological properties. Studies point to an inhibitory effect on the NMDA receptor and on fibroblast proliferation, which together suggest an anti-arthritic effect. There is an increase in NO production, macrophage activation and a reduction in pro-inflammatory cytokines, which confers anti-inflammatory properties. The cytotoxic effect of the leaves is accompanied by an antiproliferative action, both of which are relevant in anti-cancer treatment. The blood pressure lowering effect with bradycardia is

explained by agonism on type 2 muscarinic receptors. The leaves are biocompatible, promote osseointegration, osteoinduction and bone regeneration, suggesting a potential use as a bone graft.

Figure 1. Biological properties and main mechanisms of action described for *Dysphania ambrosioides* leaves



Source: Elaborated by the authors

Dysphania ambrosioides and Intellectual property protection

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1 TECHNOLOGICAL PROSPECTION FOR *D. AMBROSIOIDES* LEAVES

There are in the search databases of patents, deposits or patents granted to different pharmaceutical compositions for *D. ambrosioides*. However, most refer to the patents of the total herb structure. Table 3 lists the patents deposited or granted for *D. ambrosioides* leaves, these deposits corroborate in the validation of therapeutic potential and technological innovation referring to its use. The products act on the uterine fibroids, dental treatment, and bone graft. Brazil stands out in this context due to its elevated of patent applications for *D. ambrosioides* leaves.

Table 1: List of patents of *Dysphania ambrosioides* leaves

Application Number/ Priority date	Title	Description
US6841175B2/ 2005-01-11	*Chenopodium ambrosioides* extract for treating uterine fibroids	A method of treating abnormal growths in a patient. The growths include cancers, tumors, fibroids, cysts, and cystadenomas. Dry leaves and stalks of a Chenopodium ambrosioides plant into a dried tea. Brew the dried tea in boiled water into a tea beverage. Administer the tea beverage to the patient by having the patient drink the tea daily. The method also reduces high PSA counts.
BR 10 2016 029525 4/ 15-12-2016	Composition with healing, anti-inflammatory and antibiotic properties for dental treatment	The present invention deals with a composition with healing, anti-inflammatory and antibiotic properties for dental treatment using essential oil and crude extract of Chenopodium ambrosioides L., the latter being in lyophilized form associated with a viscous hydrosoluble vehicle such as natrosol and propylene glycol, facilitating the intra-canal and / or intraosseous application of a topical medicament with anti-inflammatory and healing action, as well as antibacterial action on Enterococcus faecalis, which supports endodontic treatment in cases with periapical and periradicular bone involvement, in situations that an accelerated cicatricial process of the periodontal tissues and oral mucosa is needed and in the surgical treatments being applied in the bone stores.
BR 10 2013 000137 6/ 17-12-2012	Pharmaceutical compositions based on *Chenopodium ambrosioides* extract and its use as an anti-inflammatory and healing agent	The present invention relates to the development of novel pharmaceutical formulations characterized in that they contain from 0.0025mg to 50000mg of leaf powder or dry extract, preferably 2.5 to 5% of the ethanolic extract of Chenopodium ambrosioides conveyed in the various pharmaceutically acceptable forms for oral, parenteral or topical use, for prophylactic and therapeutic purposes in inflammatory and tissue healing processes for use in humans and animals.
PI 1101651-5/ 12/04/2011	Process for obtaining lyophilized aqueous extract from the aerial parts of *Chenopodium ambrosioides*, formulation of pharmaceutical composition and its use as a bone graft	The present invention relates to the method of obtaining a pharmaceutical composition formulation and its use as a bone graft. The formulation is initially produced from the extract obtained from the fresh leaves in distilled water, or other solvents such as ethanol, cereal alcohol, methanol, and others of equivalent polarity, concentrated under reduced pressure, freeze-dried, of the species Chenopodium ambrosioides. The pharmaceutical composition containing the dry residue has therapeutic use of the composition in the treatment of fractures. In extensive bladder lesions, a graft derived from natural products may be used as an alternative therapy in the repair of bone defects.

2 PROSPECTS

The presence of different classes of secondary metabolites in the leaves of *D. ambrosioides* can justify the most diverse uses in the treatment of human diseases and contribute for evaluation of the pharmacological efficacy in the plant species in various biological assays and preclinical studies. Different phytochemical characterization studies provide better control of the quality of leaves, evidence the main and secondary chemical constituents that, together, act on signaling pathways in

various pathophysiological processes. Thus, for the qualitative identification of the leaves, the HPLC-MS, NMR, and GC-MS methods must be integrated into the different extraction processes.

We demonstrate in summary form that many properties attributed by the population to *D. ambrosioides* already present their scientific validation performed in vitro and in vivo assays. Furthermore, the preparations obtained from the leaves are safe for internal use and do not present toxicological risks for oral exposure. This demystifies reports of the herb toxicity in the literature, where these refer to the consumption of the entire plant.

In addition, ethanol, methanol, and aqueous extracts express different biological potentials. Bioactive compounds are entrained by these solvents and are suggested as active components of the various biological potentials of the leaves, highlighting the potential anti-tumor, antioxidant and hypotensive in rats, and bone graft in rabbits.

However, pharmacological studies are not useful in clarifying the molecular mechanisms of active components of the leaves, as well as their synergistic or antagonistic effects presents in the Phyto complex.

Therefore, it is necessary to more preclinical advances for *D. ambrosioides* leaves and its constituents to clarify the possible pharmacological targets and to open possibilities for future clinical trials.

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