UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE
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PHARMACOLOGICAL ACTIVITY OF *Ipomoea asarifolia* (Desr.) Roem. e Schult. (Convolvulaceae): A SYSTEMATIC REVIEW.

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Trabalho de conclusão de curso apresentado ao Departamento de farmácia da Universidade Federal do Rio Grande do Norte, como requisito parcial para a obtenção do título de Bacharel em farmácia.

Orientador: Prof. Dr. Matheus de Freitas Fernandes Pedrosa

Coorientador: Janaínna Xavier Fernandes

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Prof. Dr. Matheus de Freitas Fernandes Pedrosa

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PHARMACOLOGICAL ACTIVITY OF *Ipomoea asarifolia* (Desr.) Roem. e Schult. (Convolvulaceae): A SYSTEMATIC REVIEW.

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ABSTRACT

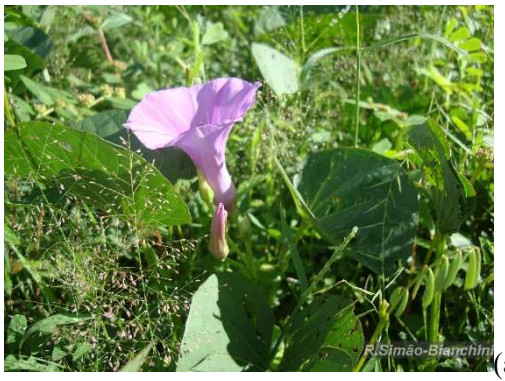
Ipomoea asarifolia is a creeping plant belonging to the genus *Ipomoea* and family Convolvulaceae, it grows spontaneously on dunes and is commonly found in South and Central America, West Africa, and tropical South Asia. Extensive pharmacological activity has been reported from the popular use of this plant to treat dermatitis, scabies, syphilis, and skin ulcers. However, there are few studies reporting or investigating the bioactive components and pharmacological activity of this plant species. Therefore, the aim of this review was to gather information about the pharmacological activity of *Ipomoea asarifolia* obtained through experimental research published until March 2022 being found reports of antioxidant, anti-inflammatory, trypanocidal, hepatoprotective, anticholinesterase and ovicidal activity. With this review, it was observed that *I. asarifolia* has pharmacological activities and that there are few studies related to the chemical composition, safety and toxicity profile of this plant species, for the development of a herbal medicine.

Palavras-chave: *Ipomoea asarifolia,* convovulaceae, salsa, antioxidant, anti-inflammatory, trypanocidal, hepatoprotectant, anticholinesterase, ovicidal.

1. Introduction

The use of plants to treat illness is an ancient practice that has been passed down from generation to generation. Although medical advances are constant and new drugs are developed, 85% of the population in developing countries seek medicinal plants and their preparations in primary care as a more affordable alternative to improve their pathological condition (Brasil, 2016).

Ipomoea asarifolia is a creeping plant of the genus *Ipomoea* and family Convolvulaceae, being considered a weed, commonly found in South and Central America, West Africa and tropical South Asia. In Brazil, it is found in the Amazon, Caatinga and Atlantic Forest (Simão-Bianchini and Ferreira, 2015). This plant species is present on the banks of rivers and on the coast of northern and northeastern Brazil, having an important function in sustaining the dunes (Martins et al., 2012; Simão-Bianchini and Ferreira, 2015). It is popularly known as salsa, batata brava, batatão, salsa-brava or batatarana, and is visually characterized by its reniform and deltoid leaves and by having the aerial parts lying on the ground (Figure 1) (Delgado Júnior; Buril; Alves, 2014).



(a)


(b)

Figure 1. *Ipomoea asarifolia* (Desr.) Roem. and Schult.

(a) aerial parts of the plant and flower and (b) leaf. Source: Flora e Funga do Brasil, 2022.

Although present on most continents *I. asarifolia* is used in folk medicine, mainly on the African continent, for the treatment of gynecological disorders during pregnancy, hemorrhages, ophthalmia, headaches, and stomach aches. The poultice is applied to wounds and the flowers boiled together with beans for the treatment of syphilis symptoms (Keharo and Adam, 1974). Its toxicity is related only to intoxication of ruminants, it is described in the literature, but the toxin that is present in the plant and causes a thermogenic syndrome in these animals is not known (Medeiros et al. 2003). There are studies related to the chemical composition of the plant that presents in the leaves saponins, flavonoids, phenols, tannins, alkaloids (Lima et al., 2014; Furtado et al., 2016).

Due to the wide pharmacological activity of *I. asarifolia*, observed by the popular use of the plant, and its potential for the development of a future phytotherapeutic, the aim of this review is to gather experimental research conducted so far available in the literature on the pharmacological activity of the plant species.

2. Material and Methods

To prepare the systematic literature review, the databases ScienceDirect (https://www.sciencedirect.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Knowledge (http://apps.webofknowledge .com), and Public Domain (http://www.dominiopublico.gov.br/pesquisa/PesquisaPeriodicoForm.jsp) were searched, including scientific articles, dating from 1978 to March 2022.

As search strategy we used the scientific name, synonyms and main popular names identified through the botanical bases Trópicos (http://www.tropicos.org), Flora do Brasil (http://floradobrasil.jbrj.gov.br), The plant list (http://www.theplantlist.org), KEW (Royal botanic gardens) (https://powo.science.kew.org/) and NCBI (http://www.ncbi.nlm.nih.gov/taxonomy) and the key words used were: "batata-brava" OR "batatão" OR "salsa-brava" OR "batatarana" OR "salsa" OR "*Ipomoea asarifolia (Desr.) Roem. & Schult*." OR "Amphione asarifolia Raf." OR "Convolvulus asarifolius Desr." OR "Convolvulus beladambu Spreng." OR "Convolvulus rugosus Rottler" OR "Convolvulus urbicus Salzm. ex Choisy" OR "*Ipomoea beladamboe Roem. & Schult*." OR "*Ipomoea crassifolia Cav*." OR "*Ipomoea grisebachii Prain*" OR "*Ipomoea latifolia M. Martens & Galeotti*" OR "*Ipomoea nymphaeifolia Griseb*." OR "*Ipomoea pes-caprae var. heterosepala Chodat & Hassl*" OR "*Ipomoea rubrinervia Goebel*" OR "*Ipomoea rugosa (Rottler) Choisy*" OR "*Ipomoea urbica Choisy*" OR "*Ipomoea urbica var. muricata Choisy*". The abstracts of 80 scientific articles were read. Of these, 48 were excluded because they dealt with intoxication of ruminants by the plant, and did not have data that fit the theme of this study. Of the 32 remaining articles, 23 were excluded for not having data related to the pharmacological action of *Ipomoea asarifolia*, because they reported the popular use of the plant and its botanical characteristics. Thus, the review was built based on 9 articles that met the established criteria.

3. Results and Discussion

3.1. Chemical Constituents

Phytochemical screening was conducted with the hydroethanolic extract of *Ipomoea asarifolia* leaves and showed the presence of saponins, tannins, flavonoids, phenols, reducing sugars, glycosides, terpenoids, steroids, and flobatanins (akindele; Unachukwu; Osiagwu, 2015) and with the methanolic extract of the leaves which showed alkaloids, glycosides, flavonoids, terpenes, sterols, resins, phenols, and volatile oils (Farida et al., 2012). Phytochemical analyses were performed with the aqueous extract of *Ipomoea asarifolia* leaves, being identified phenols, tannins, alkaloids, saponins and flavonoids (Furtado et al., 2016; Lima et al., 2014). Analyses performed Lima et al., (2014) with the aqueous extract and ethyl acetate fraction, using thin layer chromatography (TLC) identified the flavonoid rutin. Subsequently, the presence of this flavonoid was confirmed by Furtado et al., (2016) who, using the aqueous extract of the leaves,

through qualitative analysis of high performance liquid chromatography (HPLC-DAD) and liquid chromatography diode array detector coupled with mass spectrometry analysis (LC-DAD-MS), in addition to rutin, identified the phenolic compounds chlorogenic acid and caffeic acid. When analyzing the chemical constituents present in the essential oil of *I. asarifolia* leaves Da Silva Júnior et al., (2021) could identify the presence of phytol derivatives being present in higher content in the dry season.

3.2. Toxicity

There are few studies related to the toxicity of *Ipomoea asarifolia* extracts. The study conducted by Lima et al. (2014) showed that lower concentrations of the extract (0.25, 0.375, 0.5, 0.75, 1, 1.25, and 1.75 mg/ml in 48 and 72h) did not show significant cytotoxicity in cell culture (3T3). When conducting the study to determine the lethal dose, Farida (2012) administered the methanolic extract of the leaves at a dose of 300mg/kg, and subsequently 2000mg/kg, and it was observed that the lethal dose is higher than 2000mg/kg as there was no lethality in the mice tested. However, it was observed that the extract presented hepatotoxicity at a dose of 400 mg/kg. To evaluate acute and chronic toxicity, Akindele et al. (2015) used the hydroethanolic extract of the leaves by administering 5g/kg of the extract orally in rats, and no signs of toxicity were observed within 24h after administration. However, intraperitoneal administration of the extract at doses of 250, 500, 1000, 2000, and 4000 mg/kg, revealed that the dose required to kill 50% of the test mice (LD50) was 1000 mg/kg. In this sense, the data suggest that doses up to 300 mg/kg of the methanolic extract of the leaves, do not cause toxic or hepatic damage and doses up to 5 mg/kg of the hydroethanolic extract are not lethal if administered orally, being necessary further studies to better characterize the toxicity of this plant species.

3.3. Pharmacological activity

Few studies have characterized the pharmacological effects of *I. asarifolia* in the literature, highlighting the importance of the present research in gathering the findings on the plant (Table 1). Among the activities found are antioxidant, anti-inflammatory, trypanocidal, hepatoprotective, anticholinesterase and ovicidal. Moreover, the aqueous extract of the leaves is the most used part of *I.asarifolia*.

Tabela 1 – Componentes bioativos e propriedades farmacológicas da *I. assarifolia.*

ACTIVITY	PLANT PART	SUBSTANCES	EXTRACT	REFERENCE
Antioxidant *in vitro*	Leaves Stem and Root	Unspecified	Aqueous extract	(Ene-ojoatawodi & onaolapo, 2010)

Antioxidante *in vitro*	Leaves	Saponins, tannins, flavonoids, phenols, reducing sugars, glycosides, terpenoids, steroids, and flobatanins	Hydroethanolic extract	(Akindele; Unachukwu; Osiagwu, 2015)
Anti-inflammatory *in vivo*	Leaves	Phenols, tannins, alkaloids and flavonoids (rutin)	Aqueous extract	(Lima et al., 2014)
Anti-inflammatory *in vivo*	Leaves	Phenols (chlorogenic acid and caffeic acid), tannins, alkaloids, saponins, and flavonoids (rutin).	Aqueous extract	(Furtado et al., 2016)
Anti-inflammatory *in vivo*	Leaves	Unspecified	Aqueous extract	(Da silva et al., 2018)
Anticholinesterase *in vitro*	Leaves	Unspecified	Methanolic extract	(Feitosa et al., 2011)
Hepatoprotective *in vivo*	Leaves	Alkaloids, glycosides, flavonoids, terpenes, sterols, resins, phenols, and volatile oils	Methanolic extract	(Farida et al., 2012)
Ovicide *in vitro*	Seeds	Unspecified	Saline extract	(Salles et al., 2014)

Trypanocidal *in vitro*	Unspecified	Unspecified	Ethanolic extract	(Alkali et al., 2015)

3.3.1 Antioxidant Activity

The antioxidant activity was evaluated by Akindele et al. (2015) using albino rats and mice, where the control group used distilled water, and demonstrated that the use of the hydroethanolic extract of *Ipomoea asarifolia* leaves at concentrations of 40mg/Kg 200mg/Kg and 1000 mg/Kg caused an increase in antioxidant enzymes, reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in rats, with the 1000mg/Kg dose showing a significant increase of reduced glutathione (GSH) in the kidney. The author left some animals without using the extract for thirty days to perform the reversibility study, which revealed an increase in the levels of GHS in the brain (1000 mg/kg) and lungs (40mg/kg), of GSH and SOD in the spleen, of CAT in the heart. Showing that the extract has a potential antioxidant activity.

The aqueous extract of *Ipomoea asarifolia* showed significant antioxidant capacity through the 2,2-diphenyl-1-picrylhydrazyl radical scavenging (DPPH) method, using ascorbic acid as a standard antioxidant. In the study conducted by Ene-OjoAtawodi and Onaolapo (2010), 1g of the dried stem bark, leaves and root bark was used to produce the aqueous extract. The average antioxidant activity of the extracts of each plant part, showed an ascorbic acid equivalent of 1.7mM, and the stem bark, leaves and root peels showed respectively an IC50 (the substrate concentration that causes 50% inhibition of DPPH activity) of 42, 65 and 50 µL/mL, showing that the stem bark of *I. asarifolia* has a higher antioxidant potential. Silva et al. (2018) showed that the aqueous extract of the leaves at a dose of 100mg/kg increased the levels of the glutathione molecule and reduced the levels of the oxidative marker malonyldialdehyde (MDA), reinforcing the antioxidant power of the aqueous extract of *I. asarifolia*.

3.3.2 Anti-Inflammatory Activity

Anti-inflammatory activity is the highest activity reported in the literature for *Ipomoea asarifolia*. The aqueous extract and dichloromethane, ethyl acetate and n-butanol fractions of *Ipomoea asarifolia* leaves were evaluated by Lima et al. (2014) in relation to inflammation induced by *Tityus serrulatus* venom, being administered the venom intraperitoneally in mice. In this study, the aqueous extract of the leaves at doses of 10, 20 and 30 mg/kg caused a decrease in inflammatory cytokines (IL-6, IL-12 and IL-1) and cell migration to the site of inflammation. The dichloromethane, ethyl acetate, and n-butanol fractions were evaluated at a dose of 20 mg/kg and also obtained results similar to the aqueous extract. Regarding the dose-response profile, the

aqueous extract at doses of 10, 20, and 30 mg/kg and the ethyl acetate fraction at doses of 10, 15, and 20 mg/kg did not show a significant difference in relation to the anti-inflammatory action at the different doses tested, indicating that the anti-inflammatory effect is not dose-dependent. In addition, the flavonoid rutin at doses of 2, 2.5, and 5mg/Kg, was able to reduce cell migration along with a decrease in pro-inflammatory cytokines especially at the dose of 5mg/Kg.

Da Silva et al. (2018), revealed intestinal anti-inflammatory activity of *Ipomoea asarifolia* after pretreatment (3 days before inflammation induction) in mice with doses of 25, 50 and 100 mg/kg orally of the aqueous extract of *Ipomoea asarifolia* leaves. After induction of inflammation with 2,4-dinitrobenzene sulfonic acid intracolonic route, the pre-treatment with aqueous extract of the plant species promoted a reduction of intestinal inflammation, especially at doses of 50mg/kg and 100mg/kg, showing a better aspect of intestinal tissue and preservation of the mucous layer in relation to the group not pre-treated with the extract.

When evaluating the anti-inflammatory properties of the aqueous extract of *Ipomoea asarifolia* leaves in the carrageenan-induced paw edema model, Furtado et al, (2016) showed the ability of the extract to reduce leukocyte migration to the lesion site by 70%; 78% and 83% at doses of 10mg/kg, 20mg/kg, 30mg/kg, respectively, promoting a reduction in the levels of the cytokines L-1β, IL-6, IL-12 and TNF-α, similarly, to dexamethasone 0.5 mg/kg. Similar effect was observed for the majority compounds from the leaves of this plant species, rutin, chlorogenic acid and caffeic acid, at doses of 2, 2.5 or 5 mg/kg. In the zymosan-induced air sac inflammation model, the aqueous extract was administered beforehand, and observed a significant reduction of leukocyte migration into the formed air sac by 58%, 67% and 53% for doses of 20, 30 and 40 mg/kg, respectively, revealing a similar effect to dexamethasone (2 mg/kg), rutin and chlorogenic acid (2.5, 5 or 10 mg/kg) and caffeic acid (5, 10 or 15 mg/kg). In the xylene-induced ear edema model, the previous administration of the aqueous extract of the plant leaves at doses of 20, 30 and 40 mg/kg induced a reduction of edema by 81.69 % 85.94% and 86.44% respectively, in relation to the group that did not receive the extract, with superior effect to dexamethasone 0. 5mg/kg that reduced edema by 79.84% and similar to the isolated compounds: rutin 10mg/kg, with edema reduction of almost 98%, chlorogenic acid with 86% reduction and up to 90% reduction for caffeic acid.

3.3.3 Trypanocidal Efficacy

The study of Alkali et al., (2015) shows that in vitro the ethanolic extract of *Ipomoea asarifolia* showed a non-competitive inhibition by the enzyme phospholipase A2, which is present in the parasite *Trypanosoma evansi*, and at high concentrations, is toxic to the cell membrane. the study revealed that the extract at the concentrations of 9.4 mg/mL and 16.2 mg/mL decreased from 22.4/h to 16.5 and 9.8/h respectively, the rate of inhibition of the enzyme. The extract

showed an enzyme inhibition constant of 2.0 x 10^2 µg/mL, showing that there is a good affinity between the two. These results show that this plant species can at concentrations of be further explored, to possibly, develop an antidote for *T. evansi*.

3.3.4 Hepatoprotective activity

The methanolic extract of *Ipomoea asarifolia* leaves showed a potential hepatoprotective activity in the study conducted by Farida (2012), where it was administered, 100 mg/kg, 200 mg/kg and 400 mg/kg of the methanolic extract of the leaves, in rats, being administered the hepatotoxin CCl4 in the pre and post treatment assay with the extract. Hepatotoxin CCl4 caused liver damage such as elevation of serum alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and bilirubin levels, decreased albumin synthesis, and also impaired cholesterol metabolism and triglyceride transport. There was a hepatoprotective effect when administering the extract at the doses of 100mg/kg and 200mg/kg, by reducing the elevated serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, triglycerides, serum bilirubin, cholesterol, and liver weight, and increased serum albumin levels. However, the 400mg/kg dose showed hepatotoxic activity by increasing histopathological damage to the liver.

3.3.5. Anticholinesterase activity

Ipomoea asarifolia showed promise when the ability of the methanolic extract of the leaves was evaluated *in vitro*, which showed an inhibitory activity of the enzyme that inactivates the neurotransmitter acetylcholine, acetylcholinesterase with an IC_{50} of 0,12 mg/mL compared to the drug galantamine (IC_{50}= 0.37 x10 $^{-3}$ mg/mL) which is a reversible selective inhibitor of acetylcholinesterase (Feitosa et al., 2011).

3.3.6 Ovicidal activity

The seeds of *Ipomoea asarifolia* were analyzed for ovicidal activity against the parasite *Haemonchus contortus*, which affects ruminants. Salles et al., (2014) showed that 0.1mg of protein of the crude saline extract of the plant seeds, obtained an inhibition rate of egg hatching, above 90%, revealing a similar profile to the drug albendazole at 0.5% that showed 84% inhibition. The crude extract was dialyzed and the fraction containing molecules greater than 12KDa showed a significantly higher rate of inhibition of hatching compared to the fraction with molecules smaller than 12KDa, indicating that low molecular weight molecules, such as proteins, peptides or secondary metabolites, are responsible for the actions cited.

4. Final Considerations

Ipomoea asarifolia showed promising therapeutic potential regarding antioxidant, anti-inflammatory, hepatoprotective, trypanocidal, ovicidal, and anticholinesterase activities. The

analyzed studies show that to obtain the pharmacological effects are commonly used the seeds, stem, root, and leaves of this plant species, the latter being the most used. The plant presents bioactive substances such as flavonoids (rutin), phenols (chlorogenic acid and caffeic acid), tannins, and alkaloids, which may be responsible for the pharmacological activity. Further studies on the relationship of the compounds found and the reported pharmacological activity should be conducted to elucidate their effect. Regarding toxicity, the studies suggest that the plant extract can be used with some safety margin, since the dose of 400mg/kg orally showed hepatotoxic effect. Thus, based on the studies presented that scientifically demonstrate the pharmacological properties of *Ipomoea asarifolia*, it is possible to highlight the pharmacological potential and its application for the generation of pharmacological and/or biotechnological products.

Conflict of interest

The authors declare that there are no conflicts of interest.

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