BIOLOGICAL ACTIVITY OF *GUAZUMA ULMIFOLIA* LAMARK.- SYSTEMATIC REVIEW

Atividade biológica da Guazuma ulmifolia Lamark.- revisão sistemática

Actividad biológica de laGuazumaulmifoliaLamark.- revisión sistemática

Revista Desafios

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Artículo de revisión

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ABSTRACT

The *Guazuma ulmifolia* Lamark (*Malvaceae*) is a non-endemic plant, popularly known as mutamba. Its leaves and roots are used in home remedies against dysentery and diarrhea, in the treatment of prostate, as a uterine stimulant and other diseases. Due to the characteristics presented and the growing interest in this species, a systematic review was carried out on the possible pharmacological and toxicological effects of *Guazuma ulmifolia* Lamark. As active compounds, the articles cited the presence of flavonoids, saponins, alkaloids, tannins, phenolic compounds and steroids in different parts of the plant and extracted with different solvents. Regarding the experimental studies, no articles were found with clinical test, and only 4 in vivo studies. About the pharmacological effects we can mention activity against leishmaniasis, hypoglycemic, anti-inflammatory, anticholinesterase, anti-obesity, antiseptic, cicatrizant and anthelmintic. The registered toxicological tests were directed against lineages of cancer cells, proving effective, however, there is a need for studies to attest the safety of *G. ulmifolia* use by the population. Therefore, it is imperative to carry out further studies to ensure the use of this plant, to know doses and form of indication, as well as clinical studies in order to guarantee a correct therapy.

Keywords: *Guazuma ulmifolia*, toxicity, medicinal plants.

RESUMO

A *Guazuma ulmifolia* Lamark (Malvaceae) é uma planta não endêmica, popularmente conhecida por mutamba. Suas folhas e raízes são empregadas em remédios caseiros contra disenteria e diarreias, no tratamento de próstata, como estimulante uterino e outras enfermidades. Em virtude das características apresentadas e o crescente interesse por esta espécie, tanto para fins medicinais como alimentício, realizou-se uma revisão sistemática sobre os possíveis efeitos farmacológicos e toxicológicos da *Guazuma ulmifolia* Lamark. Como compostos ativos, os artigos citaram a presença de flavonoides, saponinas, alcaloides, taninos, compostos fenólicos e esteróides em diferentes partes da planta e extraídos com diferentes solventes. Quanto aos estudos experimentais, não foram encontrados artigos com teste clínico e, apenas 4 estudos com testes in vivo. Dos efeitos farmacológicos encontrados, pode-se citar atividade contra leishmaniose, hipoglicemiante, antiinflamatório, anticolinesterásico, antiobesidade, antisséptico, cicatrizante e anti-helmíntico. Os testes toxicológicos registrados foram direcionados contra linhagens de células cancerígenas mostrando-se efetivo, porém, há necessidade de estudos para atestar a segurança de uso de *G. ulmifolia* pela

população. Logo, apesar de utilizada, é imperativa a realização de mais estudos para assegurar o uso desta planta pela população e conhecer doses e forma de indicação, além de estudos clínicos que garantam uma correta terapêutica.
Palavras-chave: *Guazuma ulmifolia,* toxicidade, plantas medicinais.

RESUMEN

La Guazuma ulmifolia Lamark (Malvaceae) es una planta no endémica, popularmente conocida por mutamba. Sus hojas y raíces son empleadas em remédios caseros contra disentería y diarreas, em el tratamiento de próstata, como estimulante uterino y otras enfermedades. Em virtud de las características presentadas y el creciente interés por esta especie, tanto para fines medicinales como alimenticios, se realizó una revisión sistemática sobre los posibles efectos farmacológicos y toxicológicos de la Guazuma ulmifolia Lamark. Como compuestos activos, los artículos citaron la presencia de flavonoides, saponinas, alcaloides, taninos, compuestos fenólicos y esteroides en diferentes partes de la planta y extraídos con diferentes solventes. Encuanto a los estúdios experimentales, no se encontraron artículos conprueba clínica y, sólo 4 estudios conpruebas in vivo. De los efectos farmacológicos encontrados, se puede citar actividad contra leishmaniasis, hipoglicemiante, antiinflamatorio, anticolinesterásico, antiobesidad, antiséptico, cicatrizante y antihelmíntico. Las pruebas toxicológicas registradas se dirigieron contra los linajes de las células cancerígenas que se mostraron efectivos, pero hay necesidad de estudios para certificar la seguridad de uso de G. ulmifolia por la población. Por lo tanto, a pesar de ser utilizada, es imperativa la realización de más estudios para assegurar el uso de esta planta por la población y conocerdosis y forma de indicación, además de estudios clínicos que garanticen una correcta terapéutica.
Descriptores*: Guazuma ulmifolia, toxicidad, plantas medicinales.*

INTRODUCTION

Vegetable products, in addition to their role as food source, clothing and housing materials, have been used in popular therapeutics as a treatment for diseases (COPETTI e GRIEBELER, 2005) from the fight against cancer to pathogenic microorganisms (CALIXTO, 2000). Studies and discoveries use knowledge about medicinal plants in search of active principles (VEIGA JR.et al., 2005), which is a promising source for the discovery of future drugs.

Many countries with significant biological diversity of resources are developing and using traditional medicinal drug solutions for disease control, providing relief of similar symptoms and obtained from allopathic medicine (HEINRICH, 2003; BANDYOPADHYAY et al., 2004).

Guazuma ulmifolia Lam. is a common species in the Brazilian cerrado, but there is also from Amazonia to Paraná, and belongs to the family Malvaceae (SOUZA e LORENZI, 2008). It is popurlaly known as "guacimo" or "mutamba" (BERENGUER et al., 2007), the property of 5 to 10 meters in height with a trunk of 30 to 50 cm in diameter, with a non-vertical cracked bark, with a white and grayish heart. The canopy has abundant branching with simple alternate leaves with petiole or short stem, of yellowish color. A leaf blade with dry texture (cardboard) with rounded base and apex acuminate (with sharp or long tip), with creased or toothed margin and protruding ribs on both sides, and densely pubescent (with small hairs) when young and glabrous or smooth when adults (JBRJ, 2017).

In Mexico, bark tea is used by indigenous people to facilitate delivery, relieve gastrointestinal pain, no treatment for asthma, fever, diarrhea and dysentery (CARVALHO 2007 apud GUÁZUMA, 2001). In Peru, besides the tea of the barks, as leaves are also employed, without treatment of renal and hepatic diseases, and against dysentery. In Brazil, bark tea is used as a sweat in cases of fever, cough, bronchitis, asthma, pneumonia and liver problems (CRUZ, 1995).

Phytochemical analyzes revealed a presence of alkaloids and tannins in the infusion of the husk

(ANDRADE-CETTO e HEINRICH, 2005). Carvalho (2007) observed the presence of isoquinolic alkaloids, triterpenic saponins, tannins and starches. Faced with characteristics presented and growing interest in this species, a review of the pharmacological and toxic products of *Guazuma ulmifolia* Lamark was carried out.

METHODOLOGY

A systematic review search was carried out in the bases PUBMED, Science Direct, Latin American and Caribbean Literature in Health Sciences - LILACS and Google Academic in the months from August to September of 2017. As search strategies we used the descriptors: "*Guazuma ulmifolia* and toxicity", "*Guazuma ulmifolia* and ethnopharmacology", "*Guazuma ulmifolia* and bioactivity" and "*Guazuma ulmifolia* and pharmacognosy", in the Portuguese and English languages, published between the years 2010 and 2017.

The research and evaluation of the articles were carried out by two independent researchers using as inclusion criteria: i) complete articles; ii) pre-clinical studies (in vivo and in vitro) and iii) clinical trials. They were excluded books, book chapters, dissertations and theses, conference abstracts, and review articles.

The review consists of three stages: (i) electronic search in the database, (ii) selection and identification of eligible articles and (iii) extraction of data from the studies included in the review.

For the third stage, a collection instrument elaborated by the authors was used, containing the following information: plant part, type of extraction, sample, test performed, result, author and year.

RESULTS AND DISCUSSION

The search resulted in 1,379 articles that met the inclusion criteria, corresponding to 1,341 articles in the Google Scholar database, 21 articles in the PUBMED database, 10 articles in the Science Direct database, and 07 articles in the LILACS database. They were excluded after analysis of their titles, 1,132 manuscripts. Subsequently, abstracts of the remaining 247 publications were analyzed with a view to applying the inclusion and exclusion criteria, aiming at the pharmacological and toxicological effects of the plant. From these, 197 manuscripts were excluded after this stage, and in 50 articles the analysis of the entire publication was performed. At the end of the process, 22 publications were included in the study (Figure 1).

As for the type of test used in the articles studied, none were performed in humans which are the clinical tests, and the majority were pre-clinical tests in vitro (Table 1). This lack of clinical trials follows the trend of studies for the search for new drugs, where many of the probable molecules or even plant extracts do not have proven biological activity in preclinical tests, and thus they are not taken to be tested in trials clinical trials.

The synthesis and main information present in the articles chosen in this review were grouped in Table 2. From the selected studies, the bioactive compounds identified by the phytochemical analysis of *G. ulmifolia* were grouped according to Table 03.

In the phytochemical evaluation, G. ulmifolia presented active components in different extracts including flavonoids, saponins, alkaloids, tannins, total phenols and steroids present in the bark, leaves, fruits and rhizome of the plant. It is suggested that the data generated can provide the basis for a wide use as a therapeutic agent (ISWANTINI et al., 2011; PELÁEZ e RODRÍGUEZ, 2016; BATUBARA et al., 2012; PATILe BIRADAR, 2013; LUNA-CAZARES, 2017),

as a source of new molecules with pharmacological activity.

Figure 1. Flowchart of the systematic data obtained on *Guazuma ulmifolia* Lamark.

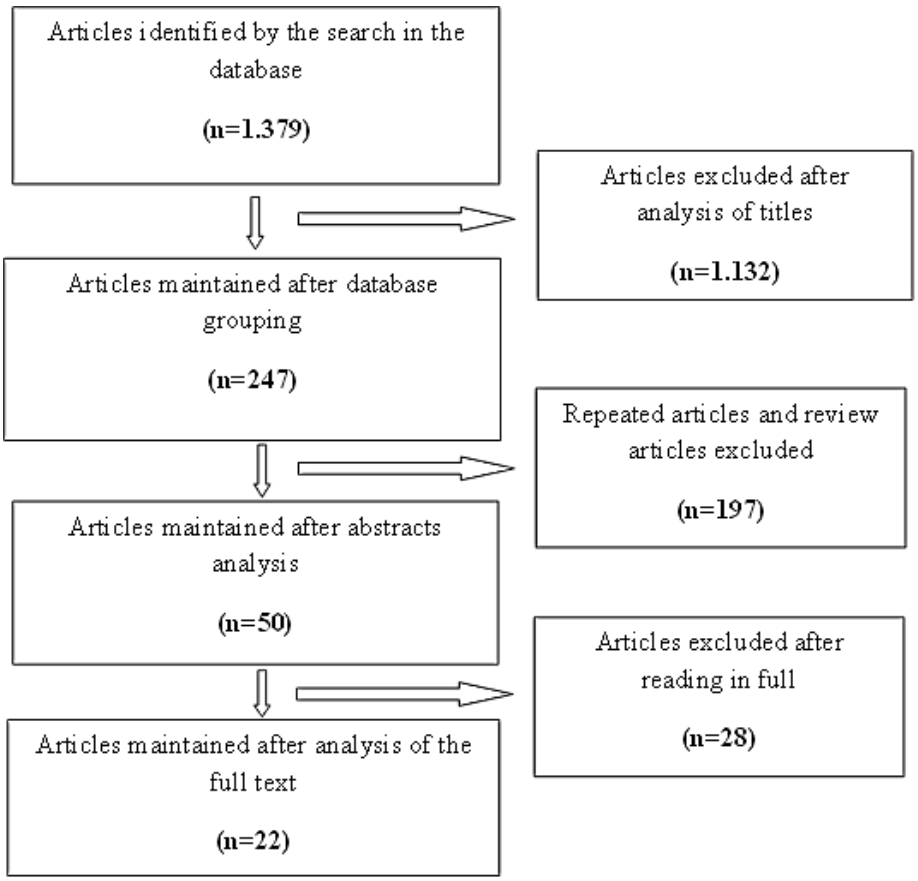

Tabela 1. Evaluation of the articles regarding the type of test performed.

Typeoftestperformed	Numberofarticles
Pre-clinical:	
In vivo	02
In vitro	18
In vivo and In vitro	02
Clinicaltest	0
Total	**22**

Table 2. Summary of articles elected.

PART OF THE PLANT	SOLVENT EXTRACTOR	SAMPLE	TEST PERFORMED	RESULT / ACTION	REFERENCE
Leaves	Hexane, Ethyl acetate and Methanol	*In vitro*	Toxicity and antioxidante activity	No toxic or antioxidant effect	Aarlandet al., 2015.
Leaves	Methanol	*In vitro*	Inhibitory activity for tumor necrosis factor (TNF-α)	Low inhibition of TNF-α	Batubaraet al., 2012.
Leaves	Hydrodistillation (H2O) to obtain essential oils	*In vitro*	Antioxidant and antimicrobial activity	Antioxidant and antibacterial effect	Boligonet al., 2013.
Leaves	Ethanol	*In vitro*	Antiparasiticactivity	Cytotoxic effect against *Trypanosoma cruzi*, *Leishmania infantum* and *Leishmania brasiliensis*	Calixto-Júnior, 2016.
Stalk	Acetone, Hexane and Methanol	*In vitro*	Antimicrobial and inhibitory activity against cancer cells	Inhibition of cancer cell activity	Cates et al., 2013.
Isolated Compound (Tyliroside)	Methanol	*In vitro*	Antiproliferative activity on cancer cells	Antiproliferative effect on cancer cells	Da'Iet al., 2016.
Leaves	Aqueous and Ethanol	*In vitro*	Inhibitory test on pancreatic lipase	Potent inhibition on pancreatic lipase	Iswantiniet al., 2011.
Leaves	Ethanol	*In vitro e in vivo*	Identification of antiglycemic compounds	Presence of glucocinin and probable effect against diabetes mellitus	Laguna-Hernandez et al., 2017.
Barks	Ethyl Acetate and Methanol	*In vitro*	Antimicrobialactivity	Antimicrobial effect	Luna-Cazares & González-Esquinca, 2017.
Barks	Hydroalcoholic	*In vitro*	Anti-inflammatoryactivity	Anti-inflammatory effect	Maldini et al, 2013.
Leaves	Hydroalcoholic	*In vitro*	Inhibitoryactivity in adipogenesis	Inhibitory effect on adipogenesis	Hidayat et al., 2015.
Barks and leaves	Ethanol	*In vitro*	Antioxidant, anticholinesterase and antifungal activity	Antioxidant effect, anticholinesterase and low antifungal effect	Morais, S. M. et al., 2017.
Leaves	Ethanol, Hexane, Ethyl Acetate and Chloroform	*In vivo*	Proliferation and differentiation of preadipocytes	Inhibitory effect on proliferation and differentiation of pre-adipocytes	Nuri et al., 2016.
Leaves and fruits	Aqueous	*In vitro*	Phytochemical screening	Active compounds have been identified	Patil & Biradar, 2013.
Leaves	Dragsteam for oil	*In vitro*	Phytochemicalscreening	Active compounds have been identified	Peláez& Rodríguez, 2016.

Continue...

PART OF THE PLANT	SOLVENT EXTRACTOR	SAMPLE	TEST PERFORMED	RESULT / ACTION	REFERENCE
Leaves	Hexane, Dichloromethane and Methanol	*In vitro*	Antifungal and antibacterial activity	Antifungal and antibacterial effect	Salcedoet al., 2014.
Leaves	Alcoholic	*In vivo*	Curing wound healing activity	Reepithelization effect	Senthil et al., 2011.
Drypowderplant	Methanol	*In vitro*	Antifungal activity	Antifungal effect	Shekhawat & Vijayvergia, 2010.
Drypowderplant	Alcoholic	*In vitro*	Anti-helminth activity	Anti-helminthic effect	Shekhawat & Vijayvergia, 2011.
Leaves, flowers, barks and fruits	Aqueous	*In vitro*	Phytochemical screening	Active compounds have been identified	Situmorang et al., 2015.
Leaves	Ethanolic	*In vitro e in vivo*	Activity on the accumulation of lipids	Inhibitory effect on the accumulation of lipids	Sulistiyani, Purwakusumah & . Andrianto, 2017.
Barks	Ethanolic	*In vitro*	Antifungal, antibacterial and toxicity test	Antifungal, antibacterial and no toxic effect	Violante et al., 2012.

Table 3. Phytochemical analyzes described in the articles analyzed on Guazuma ulmifolia Lamark.

Extraction	**Methanol**		**EthylAcetate**	**H_2O**		**Dragsteam**	**Ethanol**
Authors / **Bioactive compounds**	Batubara et al., 2012	Luna-Cazares et al., 2017	Luna_Cazares et al., 2017	Patil e Biradar et al., 2013	Iswantini et al., 2011	Peláez e Rodríguez et al., 2016	Iswantini et al., 2011
Flavonoids	$+^{A}$	$+^{C}$	$+^{C}$	$+^{A,B}$	$+^{A}$	-	$+^{A}$
Total Phenolic	$+^{A}$	$+^{C}$	$+^{C}$	-	-	-	-
Alkaloids	-	$+^{C}$	$+^{C}$	$+^{A,B}$	-	-	-
Glucosides	-	$+^{C}$	$+^{C}$	-	-	-	-
Saponin	-	$+^{C}$	$+^{C}$	$+^{A,B}$	$+^{A}$	-	$+^{A}$
Terpenes-steroids	-	$+^{C}$	$+^{C}$	-	-	-	-
Tannins	-	-	-	$+^{A,B}$	$+^{A}$	-	$+^{A}$
Terpenoids	-	-	-	$+^{A,B}$	-	-	-
Cardiacglycoside	-	-	-	$+^{A,B}$	-	-	-
Steroids	-	-	-	$+^{A,B}$	-	-	$+^{A}$
Monoterpenes	-	-	-	-	-	$+^{A}$	-
Sesquiterpenes	-	-	-	-	-	$+^{A}$	-
Aliphatic Hydrocarbons	-	-	-	-	-	$+^{A}$	-

A=Leave, B=Fruit, C=Bark, + Presence, - Absence.

In vitro assays, *G. ulmifolia* presented the most antimicrobial effect, suggesting that the presence of some chemical compounds such as flavonoids and tannins in the plant are capable of promoting the inhibition of microorganisms (VIOLANTE et al. 2012; BOLIGON et al., 2013, CATES et al., 2013, PATIL e BIRADAR, 2013). According to Shekhawat (2011), Salcedo et al. (2014), Karthika et al. (2017), Luna-Cazares e González-Esquinca (2017), the antibacterial action of natural extracts are an important source for the discovery of active molecules. Pharmacological effects of flavonoids may be responsible for the antioxidant, anticancer and antifungal actions evidenced (SHEKHAWAT e VIJAYVERGIA, 2010; BOLIGON et al., 2013, CATES et al., 2013, PATIL e BIRADAR, 2013, SALCEDO et al., 2014; DA'I et al., 2016; MORAIS et al., 2017; KARTHIKA et al., 2017).

In in vivo studies, Laguna-Hernandez et al. (2017) demonstrated that Guazuma has antihyperglycemic action, proven by histochemical analysis of the pancreas of mice. Nuri et al. (2016) detected in their assays that the ethanolic extracts from Guazuma leaves inhibit the proliferation of preadipocytes in Wistar rats. According to Sulistiyani et al. (2017) the ethanolic extract showed inhibitory activity in the accumulation of lipids under study with *Caenorhabditis elegans* (nematode). Another study using a chemically induced wound model in rats showed that leaf alcohol extract is effective in re-epithelialization and wound healing in topical use (SENTHIL et al., 2011).

Therefore, research with humans through randomized and methodologically well-conducted clinical trials should be performed to evaluate their efficacy so that they can be safely indicated in clinical practice. In addition, we can cite the low amount of pharmacokinetic, pharmacodynamic, toxicological and in vivo studies.

FINAL CONSIDERATIONS

Guazuma ulmifolia presents, in addition to popular reports of use, studies that can subsidize and justify its use in therapeutics, and as a promising source of new compounds of pharmacological interest. The main evidences of pharmacological effects related to the use of this medicinal plant were: i) antimicrobial effect; ii) antioxidant effect; iii) anticancer action and iv) antihyperglycemic. However, *in vivo* studies and clinical trials are necessary in order to assure its safety of use and to attest its therapeutic effects.

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