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Pharmacological and toxicological aspects of barbatimão (*Abarema cochliacarpos* (GOMES) Barneby & J.W. Grimes)

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Abstract**—** *Goal: To observe pharmacological and toxicological studies of Abarema cochliacarpos (GOMES) Barneby & J.W. Grimes which indicate efficacy and safety in its use as an herbal medicine. Method: Systematic review study in the BVS, PubMed and SciELO databases. The descriptors "Abarema", "cochliacarpos", "pharmacological", and "toxicological" and Boolean operator "AND" were used. Inclusion criteria: Abarema cochliacarpos (GOMES) Barneby & J.W. Grimes; pharmacological action; toxicological action. Exclusion criteria: review study and duplicated articles. The studies were analyzed regarding the in vivo characteristics (mice and rats) or in vitro (cell and bacterial lines), pharmacological or toxicological action, derived from plant drug/part of plant and authorship. Results: 11 articles selected in the review pointed out: analgesic activity tested in Swiss mice; antibacterial in lineages such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa; anti-inflammatory tested in Wistar Rats and Swiss mice; antioxidant in vitro model on oxidative damage and also in a Swiss mouse model; antiulcerogenic analyzed in Wistar rats; myoprotective in Swiss mice; estrogenic and thyroid modulation tested in cell lineage. The toxicological essay found approached the hepatotoxicity induced by A. cochliacarpos in Mus musculus mice. Conclusion: A. cochliacarpos has phytoactive constituents with analgesic action, antibacterial, myoprotective, anti-inflammatory, antioxidant, antiulcerogenic, estrogenic and thyroid modulation in animal models in vivo and in vitro, with the bark being the most used part in extracts and fractions. Faced with the need for proof of safety in the use of plants as herbal medicines, toxicological tests have to get conducted to ensure the safe use of the species, as correlated with the barbatimão.*

I. INTRODUCTION

Phytotherapy is an ancient practice based on the use of plants for medicinal purposes, with preventive and curative purposes, and its use is encouraged by the World Health Organization (WHO, 2019). The barbatimão is widely used as a medicinal plant by the population, being also

known as barba-de-timão, casca-da-virgindade, faveira and barbatimão branco. The plant species evaluated by the National Health Surveillance Agency (ANVISA) and registered for using in phytotherapy is *Stryphnodendron adstringens* (MART.) Coville. However, other related species, native or exotic are also called barbatimão: *Abarema cochliacarpos* (Gomes) Barneby & J.W. Grimes, *S. coriaceum* Benth., *S. pulcherrimum* (Willd.) Hochr. and *S. pumilum* Glaz (Brasil, 2014; Tenório, RFL., MS, JVML, & MCDOC., 2016).

The barbatimão, *Abarema cochliacarpos* (GOMES) Barneby & J.W. Grimes is a native plant from Brazil, which belongs to the family called *Fabaceae* and subfamily *Mimosoidae* (Iganci, JRV, & MP., 2012). The therapeutic properties of phytochemicals are due to active substances present in several parts of the plant, obtained as a total or processed extract. Popularly, the barks of barbatimão are used after a decoction process to heal wounds, ulcers, treatment of sore throats and bleeding (Souza-Moreira, Queiroz-Fernandes, & Pietro, 2018). These healing actions are possible for the presence of the plant phytoactive constituents. The phytochemistry analysis of barbatimão showed the presence of catechin compounds (its dimers and trimers), and others phytoconstituents such as saponins, tannins and proanthocyanidins, anthraquinones, alkaloids, flavonoids, terpenes and steroids (da Silva, Sánchez-Fidalgo, et al., 2010; A. Dias, De Araújo, De Araújo, & Estevam, 2014).

The most of plant species used in folk medicine do not have pharmacological evidence, nor toxicological studies as recommended by resolution 90/2004(Carvalho, Balbino, Maciel, & Perfeito, 2008), which governs plant toxicity studies for phytotherapeutic purposes. In addition, the designation of plants of several species with the same name (barbatimão), points to the need to verify scientific evidence of the efficacy and safety in the use as herbal medicine. This study aimed to observe pharmacological and toxicological studies of *Abarema cochliacarpos* (GOMES) Barneby & J.W. Grimes which indicate efficacy and safety in its use as an herbal medicine.

II. METHODOLOGY

2.1. TYPE OF STUDY

This is a Systematic Review study according to the Preferred Reporting Items for Systematic Reviews (PRISMA) method (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.2. STUDY LOCATION

The consulted databases were: the BVS (Biblioteca Virtual de Saúde), PubMed (National Library of Medicine – NIH) and SciELO (Scientific Electronic Library Online).

2.3. ELIGIBILITY CRITERIA

The inclusion criteria involved: (i) *Abarema cochliacarpos* (GOMES) Barneby & J.W. Grimes; (ii) pharmacological action; (iii) toxicological action. Exclusion criteria: (i) review study and (ii) duplicated articles. Thus, original research involving pharmacological and toxicological analyzes of barbatimão were selected.

2.4. INSTRUMENTS AND TECHNIQUES RESEARCH

The search was carried out on February 26, 2021, and updated on June 6, 2021. It performed analysis of all studies which were published up to the year 2021. In this study were selected articles involving pharmacological and toxicological barbatimão tests. It was used the descriptors "*Abarema*", "*cochliacarpos*", "pharmacological", and "toxicological" associated with the Boolean operator "AND".

2.5. DATA EXTRACTION

Each article was examined for eligibility by two independent evaluators. A third evaluator resolved disagreements regarding to the inclusion of articles. Data on doses of *A. cochliacarpos* used, characteristics of in vivo and in vitro research, type of pharmacological or toxicological action, derived from a plant drug/part of the plant and the authorship of the studies were extracted for two tables pre-edited by two evaluators.

III. RESULTS

Observing the pharmacological and toxicological studies of *A. cochliacarpos*, in in vitro models (cell and bacterial lineages) and in vivo (mice and rats), 100 articles were found in the databases, 44 articles in the BVS portal, 25 articles in the PubMed portal and 31 articles in the SciELO portal (**Table 1**). In compliance with the object of the study, 30 articles were excluded for not treating with *A. cochliacarpos*, or for portraying other species such as *Abarema auriculata*, *Abarema pittier* and *Pithecellobium cochliocarpum*; 14 were excluded for not being original articles and 45 articles were duplicated. Eleven articles remained to be analyzed in order to verify efficacy and safety in the use of *A. cochliacarpos* for therapeutic purposes (**Figure 1**).

Table. 1: Distribution of studies in the databases.

Search strategy	BVS	PubMed	SciELO
Abarema	23	11	22
Abarema cochliacarpos	10	6	6
Abarema AND farmacológica	6	1	0
Abarema AND pharmacological	3	5	2
Abarema AND toxicológica	0	1	0
Abarema AND toxicological	2	1	1
Total	**44**	**25**	**31**

3.1. CHARACTERIZATION OF THE STUDY

To understand the pharmacological potential of barbatimão, the original works were grouped by pharmacological activity involved in the studies, including analgesic (17%) (Saturnino-Oliveira et al., 2014; N. Silva et al., 2009), antibacterial (17%) (Santos, Ferreira, Rossi-Alva, & LG., 2007; Tenório et al., 2016), anti-inflammatory (25%) (da Silva, Sánchez-Fidalgo, et al., 2010; Sánchez-Fidalgo et al., 2013), antioxidant (17%)(A. S. Dias et al., 2013; Sánchez-Fidalgo et al., 2013), antiulcerogenic (8%)(da Silva, de Almeida, et al., 2010), myoprotective (8%) (Saturnino-Oliveira et al., 2014) and estrogenic and thyroid modulation (8%)(Reis et al., 2018) (**Fig. 2**; **Table 2**). Regarding to the toxicological potential of *A. cochliacarpos*, the found study involved the hepatotoxic activity (Oliveira et al., 2013) (**Table 3**).

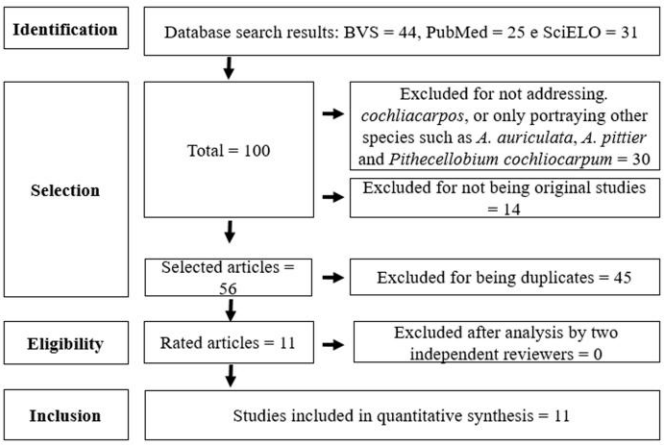

Fig.1: Study selection process to compose the review.

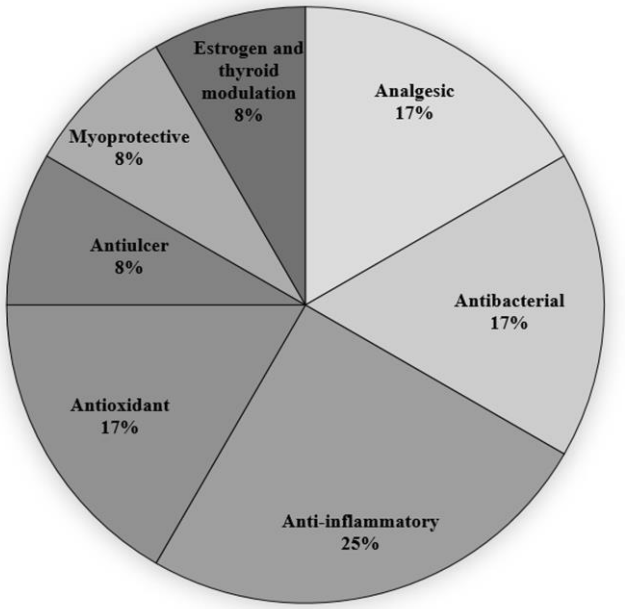

Fig.2: Pharmacological actions of A. cochliacarpos selected to compose the article.

3.2. CHARACTERIZATION OF PHARMACOLOGICAL STUDIES

3.2.1. Analgesic Activity

Saturnino-Oliveira et al.(2014) observed the anti-inflammatory action in Swiss mice treated with doses (100 and 200 mg/kg) of the hydroethanolic extract of *A. cochliacarpos* and a decrease (39%) of oedema with 400 mg/kg of the extract. When analyzed the functional motor activity in mice on the effect of *Bothrops leucurus* snake venom and treated with the extract, they observed that muscle fibers were preserved, the oedema and pain decreased and improvement in motor functional activity.

In another study (Silva et al., 2009), the analgesic action was verified through modulation in abdominal contractions induced by acetic acid, in mice treated with cold (CA) and hot (HA) aqueous extracts and methanolic (ME) extract of *A cochliacarpos* at 10 mg/kg, it occurred 73% of abdominal contortion by CA, 68% by HA and 39% by ME. The ME (10 mg/kg) also influenced the neurobiological response of animal defense reactions such as licking and/or biting when injected capsaicin, noting 62% inhibition.

3.2.2. Antibacterial Activity

The antibacterial action was tested by two studies. One of them used the hydroalcoholic extract of barbatimão at 1, 2 and 3 mg/mL doses against the following bacteria: *Staphylococcus aureus* (MIC of 0.3125 mg/mL), *Micrococcus luteus* (MIC of 0.1562 mg/mL), *Escherichia coli*, *Pseudomonas aeruginosa* and *S. aureus* (MIC of

0.3125 mg/mL) isolated from samples of infected individuals(Santos et al., 2007).

Tenório et al. (2016), tested the acetonic (EA), cyclohexanic (ECH) and ethanolic (EE) extracts of the bark (6.25; 12.5; 25; 50 and 100 mg/mL), in vitro, against *Bacillus* sp., *E. coli*, *S. intermedius* and *Pasteurella* sp. bacteria collected from dogs with trauma and bruise lacer skin loss. Phytoactive constituents of EA, ECH and EE extracts from the bark of *A. cochliacarpos* at 25; 50 and 100 mg/mL were able to inhibit the bacterial growth of the tested species.

3.2.3. Anti-inflammatory activity

Silva et al.(da Silva, Sánchez-Fidalgo, et al., 2010) pointed out the anti-inflammatory action of *A. cochliacarpos* by using the butanolic fraction (FB) of the methanolic bark extract (100 and 150 mg/kg) and used a model of acute ulcerative colitis induced by intracolonic injection of sulphonic trinitrobenzene acid (TNBS) in Wistar rats. The authors showed that FB decreased the macroscopic damages compared with TNBS in Wistar rats; through histological analysis they noticed that there was an improvement in the microscopic structure and preserved some areas of the structure of the colonic mucosa. Another study (M. Silva et al., 2011), also with the FB of the methanolic extract of barbatimão (150 mg/kg) in Wistar rats used the same colitis induction model, showing an improvement in inflammation with a decrease in the lesion and healing induction, with a decrease in TNF-α and the increasing of anti-inflammatory cytokine (IL-10).

3.2.4. Anti-inflammatory and antioxidante activity

Sánchez-Fidalgo et al.(2013) tested the butanolic fraction of the methanolic extract (12.5, 25 and 50 µg/mL) in Swiss mice. The FB at a dose 50 µg/mL reduced the inflammatory response induced by bacterial lipopolysaccharides (LPS) in murine peritoneal macrophages in in vitro cell model. Additionally, a negative regulation was observed in the expression of cyclooxygenase-2 (COX-2) and nitric oxide inducible synthase (iNOS) in cells treated with 50 µg/mL of the fraction.

3.2.5. Antioxidant activity

The antioxidant activity of the hydroethanol extract (EE) and its ethyl acetate (EAF) and hydromethanol (HMF) fractions of *A. cochliacarpos* (10, 100 and 1000 µg mL-1) against oxidative damage were analyzed by Dias et al.(A. S. Dias et al., 2013) The authors also noticed an immediate nullifying effect against peroxyl radicals induced by α,α,but-azodiisobutyramidine dihydrochloride (AAPH) when used in the total antioxidant reactivity test (TAR). The phytoactive present in the extracts and fractions showed the potential hijacking of reactive nitrogen species (RNS) reducing the formation of nitric oxide (NO) at a dose of 100 µg mL-1 (29.7% EE, 34.3% EAF and 36, 7% HMF) and 1000 µg ml -1 (52.7% EE, 18.4% EAF and 30.5% HMF).

The chloroform (200 and 400 mg/kg) and methanolic (100, 200 and 400 mg/kg) extracts and the butanolic fraction of the methanolic extract induced an antiucerogenic effect in ulcer models caused by absolute alcohol in Wistar rats. The mechanisms of action proposed by the authors involve activation of vascular endothelial growth factor (VEGF) and thermal shock protein (HSP70) and inhibition of COX-2, promoting cell proliferation, healing and regeneration of tissue injury (da Silva, de Almeida, et al., 2010).

3.2.6. Anti-ulcer activity

Chloroform (200 and 400 mg/kg) and methanol (100, 200 and 400 mg/kg) extracts and the butanolic fraction of A. cochliacarpos methanolic extract an anti-ucerogenic effect in ulcer models induced-absolute alcohol in Wistar rat. Activation of vascular endothelial growth factor (VEGF) and heat shock protein (HSP70) and COX-2 inhibition appear to be involved in cell proliferation, healing and tissue injury regeneration (da Silva, Sánchez-Fidalgo, et al., 2010).

Table 2: Dose/effect profile of A. cochliacarpos in vivo and in vitro models pharmacological.

Pharmacological activity	Vegetable drug derivative / Plant part	Dose	Model	Author
Analgesic	- Hidroethanolic extract /stem bark	100, 200 e 400 mg/kg	Male *Swiss* mice	Saturnino-Oliveira et al 2014
	- Cold aqueous extract/ stem bark - Methanolic extract/ stem bark - Hot aqueous extracts/ stem bark	3, 6, 10 e 100 mg/kg	Male *Swiss* mice	Silva et al 2009

Antibacterial	- Hydroalcoholic extract/ bark	1, 2 e 3 mg/mL	*In vitro* - *Staphylococcus aureus*, *Micrococcus luteus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *S. aureus* clinical sample isolate	Santos et al 2007
	- Acetone extract/ bark - Cyclohexane extract/ bark - Ethanol extract/ bark	6,25; 12,5; 25; 50 e 100 mg/mL	*In vitro* - *S. intermedius*, *Bacillus* sp., *Pasteurella* sp. and *E. coli*	Tenório et al 2016
Anti-inflammatory	- Butanolic fraction of the methanolic extract/stem bark	100 e 150 mg/kg	Male and female Wistar rats	Da Silva et al 2010
	- Butanolic fraction of the methanolic extract/stem bark	150 mg/kg	Male and female Wistar rats	Da Silva et al 2010
	- Butanolic fraction of the methanolic extract/ stem bark	6,25; 12,5; 25; 50.; 100 e 200 µg/mL	*Swiss* mice	Sánchez-Fidalgo et al 2013
	- Flavonoid, (+)-catechin	1,875; 3,75; 7,5; 15 e 30 µg/mL		
Antioxidant	- Ethanol extract/ stem bark - Ethyl acetate fraction of the ethanol extract - Hydromethanol fraction of the ethanol extract - Hexane fraction of the ethanol extract - Chloroform fraction of the ethanol extract	10, 100 e 1000 µg mL $^{-1}$	*In vitro* - oxidative damage	Dias et al 2013
	- Butanolic fraction of the methanolic extract/ stem bark	6,25; 12,5; 25; 50.; 100 e 200 µg/mL	*Swiss* mice	Sánchez-Fidalgo et al 2013
	- Flavonoid, (+)-catechin	1,875; 3,75; 7,5; 15 e 30 µg/mL		
Antiulcer	- Chloroform extract/ bark	100, 200 e 400 mg/kg	Male Wistar rats	Da Silva et al 2010
	- Methanolic extract/ bark			
	- Butanolic fraction of the methanolic extract - Ethyl acetate fraction of the methanolic extract - Aqueous fraction of the methanolic extract	12,5; 25, 50, 50, 100, 150 e 200 mg/kg		
Myoprotective	- Hidroethanolic extract /stem	100, 200 e 400	Male *Swiss* mice	Saturnino-Oliveira

	bark	mg/ kg		et al 2014
Estrogen and thyroid modulation	- Methanol extract/ whole plant	50 e 100 µg/mL	*In vitro* - ER and TR gene-reporter assays, using 17-estradiol and triiodothyronine as the positive controls.	Reis et al 2018

Table 3: Toxicological profile of A. cochliacarpos.

Toxicological activity	**Vegetable drug derivative / Plant part**	**Dose**	**Model**	**Author**
Hepatotoxicity	- Hydroalcoholic extract/ stem bark	125, 250, 500, 1000 mg/ mL	Mice *Mus musculus*	Oliveira et al 2009
	- 1 mL the bark infusion	12,5; 25; 50% v/v		

3.2.7. Myoprotective activity

The myoprotective effect of the hydroethanolic extract of *A. cochliacarpos* in Swiss mice was evaluated after injecting the venom of *B. leucurus* (Saturnino-Oliveira et al., 2014). The myoprotective activity was observed in the microscopic evaluation, at which the treated muscles showed preserved structures, decreasing edema and inflammatory infiltrate compared with untreated animals. It was also noted that the extract of *A. cochliacarpos* reduced the myonecrotic effect induced by the snake venom, and less areas of hypercontracted myofilaments being able to be observed or hemorrhagic components with a decrease in edema and plasmatic creatine phosphokinase activity (Saturnino-Oliveira et al., 2014).

3.2.8. Estrogenic and thyroid modulating activity

Another pharmacological activity of *A. cochliacarpos* highlighted in the studies, using the methanolic extract obtained from several parts of the plant at the doses of 50 and 100 µg/mL is the positive modulation of the thyroid, increasing gene expression, comparing the effect with classic drugs such as 17β-estradiol and triiodothyronine. Phytoactive contituents present in *A. cochliacarpos* extracts were also able to activate estrogen receptor as far as the positive control (17β-estradiol) (Reis et al., 2018).

3.3. CHARACTERIZATION OF THE TOXICOLOGICAL TEST

3.3.1. Hepatotoxic activity

The only study that presented toxicological tests during the search in the databases showed that phytoconstituents of the hydroalcoholic extract of the bark of *A. cochliacarpos* (125, 250, 500, 1000 mg/mL) and 1 mL of infusion of the plant bark, orally and nasograstric, induced hepatic steatosis (hepatotoxicity) in Mus musculus mice (R. Oliveira et al., 2013).

IV. DISCUSSION

Abarema cochliacarpos (GOMES) Barneby & JW Grimes is a related plant species of the *Stryphnodendron adstringens* (Mart.) Coville species, both popularly known as barbatimão. *S. adstringens* has a monograph organized by the Ministry of Health and ANVISA, which also deals with information on the safety and efficacy of the species in the use as an herbal medicine. However, *Abarema cochliacarpos* is identified as a correlated species of *S. adstringens*, which motivated the search for scientific evidence on its use in the phytotherapy (Brasil, 2014).

The systematic review made it possible to realize that *Abarema cochliacarpos* has phytoactive substances with antioxidant, anti-inflammatory, antibacterial, myoprotective, estrogenic and thyroid modulator activities. The indications of *S. astringens* in phytotherapy point to antinociceptive (Melo et al., 2007), antibacterial (Ferreira et al., 2010; D. Oliveira et al., 2007; Pinho, Souza, Sobrinho, Almeida, & Martins, 2012; Souza, Moreira, Pietro, & Isaac, 2007) antiinflammatory (Lima, Martins, & Junior, 1998), gastroprotective and anti-ulcer action(Audi et al., 1999; Martins, Lima, & Rao, 2002).

The acute and chronic models of inflammation, in male Wistar rats, an anti-inflammatory action of the methanolic extract of the of *S. adstringens* stem is showed (Lima et al., 1998). One of the main effects of the action of snake venom of the species *Bothrops leucurus* in the tissue, due to the inflammatory reaction (local mediators such as histamine and serotonin) is the presence of oedema and necrosis that can lead to functional loss or even

compartment syndrome (Anz et al., 2010). The increased sensitivity to painful stimuli after the induction of this venom and the lack of antibotropic serum that neutralizes this shows the importance of studies in the area and the development of therapeutic processes to control hyperalgesia (Picolo, Chacur, Gutiérrez, Teixeira, & Cury, 2002).

A gastric disease that affects many people is the peptic ulcer, which can be caused by reasons such as stress, alcohol, smoking, use of medications, among others. The gastroprotective effects of barbatimão in a stress gastric injury model was also tested in male Wistar rats by using extracts (100 and 400 mg/kg) of the bark of stem of the *S. adstringens (Audi et al., 1999; Martins et al., 2002)*.

The monograph of *S. adstringens* (Brasil, 2014) does not approach studies with hepatotoxic action, but it is noteworthy that as the use of the infusion of the bark of barbatimão is widely popularly used to treat gastric conditions, it is necessary to carry out more studies on this respect because its use without a safe dosage can cause liver diseases(Rebecca et al., 2003). As the present data indicate, the regularization of the phytotherapy requires ethnobotany evidence, laboratory studies and pre-clinical tests necessary to ensure efficacy and toxicological tests recommended to ensure safety.

V. CONCLUSION

Pharmacological studies on *A. cochliacarpos* showed considerable heterogeneity in the pharmacological actions identified as analgesic, antibacterial, myoprotero, anti-inflammatory, antioxidant, antiulcerogenic and estrogenic and thyroid modulation. The studies involved in vivo and in vitro animal models, with the bark of the plant being the most used part in extract and fraction production. Among 11 selected studies, only one study carried out a toxicological test, in which the hepatotoxicity of *A. cochliacarpos* was scored. In this sense, further studies on *Abarema cochliacarpos* (GOMES) Barneby & J.W. Grimes have to get conducted so that they can be used as a safe and effective correlated phytotherapeutic efect of *Stryphnodendron adstringens*. It is also important to prove its safety for using in folk medicine or phytotherapy in the long term, as the use of barbatimão can also be a cause of intoxication depending on the dose used and the time of use.

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