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PHYTOCHEMICAL CHARACTERIZATION AND ANTIOXIDANT AND ANTIMICROBIAL ACTIVITY OF HYDROALCOHOLIC EXTRACT OF *MORUS ALBA* LEAVES

Ingrid Araújo Barbosa[1], Érica Menezes Rabelo[2], Ana Luzia Ferreira Farias[3], Patrick de Castro Cantuária[4] and Sheylla Susan Moreira da Silva de Almeida[5*]

[1]Laboratório de Farmacognosia e Fitoquímica, Universidade Federal do Amapá. 0000-0003-0609-4274. Macapá, AP, Brasil.
[2]Laboratório de Farmacognosia e Fitoquímica, Universidade Federal do Amapá. 0000-0003-0863-115. Macapá, AP, Brasil.
[3] Laboratório de Farmacognosia e Fitoquímica, Universidade Federal do Amapá. 0000-0002-5338-6598. Macapá, AP, Brasil.
[4]Herbário Amapaense, Instituto de Pesquisas Científicas e Tecnológicas do Estado do Amapá. 0000-0002-3676-7866. Macapá, AP, Brasil.
[5]Laboratório de Farmacognosia e Fitoquímica, Universidade Federal do Amapá. 0000-0002-7687-8288. Macapá, AP, Brasil.

***Corresponding Author: Sheylla Susan Moreira da Silva de Almeida**
Laboratório de Farmacognosia e Fitoquímica, Universidade Federal do Amapá. 0000-0002-7687-8288. Macapá, AP, Brasil.

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ABSTRACT
The white mulberry, *Morus alba*, is a species of plants belonging to the genus *Morus*, of the Moraceae family. This plant genus has secondary metabolites that are precursors for the development of biological and pharmacological activities by the plant. The objective of this work was to evaluate the metabolites present in the crude hydroalcoholic extract of the mulberry leaves and to analyze their antioxidant and antimicrobial properties. The performance of the phytochemical tests consisted of colorimetric and/or standard precipitation procedures. For the antioxidant activity, the methodology used was based on the 1,1-diphenyl-2-picrylhydrazyl (DPPH) technique, and the antimicrobial activity consisted of an agar diffusion test for *Staphylococcus aureus*, and by determining the concentration minimal inhibitory (MIC). Through the characterization of these compounds, the presence of antioxidant and antimicrobial biological activities can be presumed, obtained by the action of flavonoid and anthocyanin compounds.

KEYWORDS: white mulberry, flavonoids, anthocyanins, medicinal plant, antimicrobial.

INTRODUCTION
Brazil has extremely rich biodiversity in plants that have biological activities inherent to the healing properties, being studied as to their use for health benefits based on indigenous knowledge, which is a very wide field, and empirical phytotherapy, which are common senses of society passed down from generation to generation (Lopes 2015).

An example is mulberries, plants belonging to the genus *Morus*, of the Moraceae family. They are medium-sized trees, measuring up to three meters in height; containing cylindrical-shaped fruits, considered aggregated fruits originating from flowers (Piekarski 2013). These fruits contain reserves of sugars and organic acids, and, according to studies, great genetic variability, giving the genus presentations of morphological changes according to the ecological conditions of cultivation (Kafkas 2008).

The genus *Morus* comes from Asia, is widely cultivated in countries like China and Japan, due to its use as food for the silkworm (*Bombyx mori*), in addition to its use in traditional Chinese medicine used for acting as a hepatoprotective agent, hypotensive, antipyretic, analgesic and diuretic (Oliveira 2013). It is a genus that has sources of secondary metabolites that have biological and pharmacological activities, such as flavonoid compounds and anthocyanins (Piekarski 2013).

Based on the variety of uses of plants of the genus *Morus*, and their medicinal and pharmacological properties, the objective of this research was to evaluate the metabolites present in the hydroalcoholic extract of mulberry leaves and to evaluate antioxidant and antimicrobial activities.

FAMILY MORACEAE Gaudich

The Moraceae Gaudich Family (Gaudichaud-Beaupré 1835) was first classified in the order Urticales by Cronquist (1981). The division of this order is based only on morphological aspects, such as vegetative, reproductive characters, leaves, flowers, and eggs. Humphries & Blackmore (1989) revised the classification of Moraceae Gaudich. with the first phylogenetic study for the family tribes, the same being paraphyletic. Barroso (2002) considered Moraceae Gaudich. as a single-family divided into three subfamilies: Moroideae, Artocarpoideae, and Conocephaloideae. Also based on phylogenetic data, Datwyler & Weinblen (2004) redistributed the genera of this family. In addition to this review, they proposed, based on molecular studies, that Moraceae Gaudich. it is a family belonging to the order Rosideae, close to Urticales (Ribeiro 2007).

The Moraceae Gaudich family. it has approximately 38 genera and 1150 species (Piekarski 2013). It includes shrubs, trees and herbs, inert or armed, monoic or dioic inflorescences, with the presence of dairy products throughout the plant (Romaniuc-Neto *et al.*, 2018). This family comprises broad genera such as *Ficus* L. (Linnaeus 1753) and *Dorstenia* L. (Linnaeus 1754) in addition to other important genera such as *Morus* L. (Linnaeus 1754), *Maclura* Nutt. (Nuttall, 1818), *Artocarpus* J.R.Forst. & G.Forst. (Forster *et al*. 1776) and *Broussonetia* Ortega (Ortega 1798). It is widely distributed around the world, however, its presence is more evident in tropical and subtropical areas. Some authors claim that the Moraceae Gaudich family. it needs a more detailed review of the characteristics of this group, as there is no consensus on its characteristics.

Morphological Aspects of The Moraceae Gaudich Family

The Moraceae Gaudich family has as main characteristic the diversity of inflorescences, based on numinous flowers and the inflorescence of multiple fruits and the late science of the plants belonging to this Family (Judd 2009).

Morphologically, they present alternate and simple leaves, whole or lobed. The nerve of the plant can be pinned or spanked, and are usually petiolate and with intrapeciolar stipules. The leaves are small or wide, whole or serrated, and can leave circular scars on the branch when they fall. There are evident morphological differences between young and adult leaves (Carauta 1980).

Inflorescences in pseudo-umbels can become clusters, glomeruli, ears, and umbels. The unisex flowers can be aclamid or monoaclamid, with segments of the perigone free or concrete. The tepals become fleshy and are associated with the fruit (Judd 2009; José 2015). The male flower contains perigone divided into four segments, has curved or straight stamens on the bud. The female flower has a perigone similar to the male flower, however, it has an undivided or bifurcated stylet and an ovary is infertile or semi-infertile, supercilious, and bicarpellate, unilocular, with a pendulum or basal ovum (Carauta 1980; Ribeiro 2007).

The fruit can be drupaceous or in achenes, usually joined in syncopes. The seeds may contain the endosperm and the embryo may be straight or curved, with thick, folded or flat cotyledons, sometimes unequal (Carauta 1980).

Moraceae Gaudich. In Brazil

The Moraceae Gaudich family. it is very common in tropical and humid environments. According to Romaniuc-Neto *et al.* (2018), Brazil covers about 19 genera and 205 species. Among these, the genera *Artocarpus* J.R.Forst. & G.Forst., *Bagassa* Aubl (Aublet 1775), *Batocarpus* H. Karst. (Karsten 1858), *Brosimum* Sw. (Swartz 1788), *Castilla* Cerv. (Cervantes 1794), *Cecropia* Lofl. (Lofling 1758), *Clarisia* Ruiz & Pav. & Lanj. (Lanjouw 1936), *Maclura* Nutt., *Coussapoa* Aubl. (Aublet 1775), *Dorstenia* L., *Ficus* L., Helianthostylis Baill. (Baillon 1861), *Helicostylis* Trécul. (Trécul 1896), *Maquira* Aubl. (Aublet 1775), *Morus* L., Perebea Aubl. (Aublet 1775), *Pseudolmedia* Trécul. (Trécul 1896), *Sorocea* A.St.-Hil. (Saint-Hilaire 1821) and *Trymatococcus* Poepp. & Endl. (Poeppig *et al.* 1845). The most common examples of this family in Brazil are plants such as jackfruit and breadfruit (*Artocarpus* sp.), Fig and gameleira (*Ficus* sp.) And mulberries (*Morus* sp.).

Moraceae In the State of Amapá

According to Sardinha et al. (2017) and studies carried out in forest areas in the State of Amapá, the Moraceae Gaudich family. presents, together with other families, great species richness. The most common species of this family found in these areas were *Ficus numphaeifolia* L. (Linnaeus 1753), widely used as a medicinal plant and for ornamental purposes, and *Naucleopsis caloneura* Ducke. (Ducke 1922), employed in construction, edged construction in general.

Chemotaxonomic Studies of The Moraceae Gaudich Family

Chemosystematic analysis in the literature related to the Moraceae Gaudich family. have as main characteristic the high production of triterpenes, flavonoids and coumarins. Triterpenes are natural compounds belonging to the class of terpenes. They are precursors of substances such as eufol and tirucalol. They are molecules made up of 30 atoms and 6 isoprene units that are linked together, oriented in the opposite direction. The most common classes of terpenes in species of the Moraceae family are Taraxans, Lupans, Oleanos, and Ursanos (Porto 2011).

The flavonoids have a structure composed of 2 aromatic rings and an oxygenated heterocyclic ring. Its biosynthesis is based on a mixed route, with part of the structure derived from shikimic acid and another part from acetyl-CoA. The most commonly found flavonoids are quercetin, kaempferol, catechins, and anthocyanins (Pereira *et al*. 2017). These complex phenolic compounds can undergo biotransformations through modifications of side chains and hydroxyl groups. Antioxidant and anti-inflammatory activity, vasodilator effect, antiallergic, antitumor, antiviral, and antimicrobial action are examples of benefits promoted to the organism by this class of metabolites (Santos; Rodrigues 2017).

Coumarins are widely distributed in the plant kingdom (Simões *et al*. 2001). These metabolites belong to a group of phenolic substances that have a benzene ring and at least one hydroxyl group. In plants, these compounds are closely linked to their defense mechanisms (Alves 2017). These compounds have varieties in terms of their important biological activities, including antimicrobial, anti-inflammatory, antitumor, antioxidant, antiviral activity, which are related to the substance's ability to suppress reactive oxygen species (Porto 2011).

Morus alba

Mulberries are plants belonging to the genus *Morus* L., of the family Moraceae Gaudich. Approximately 16 members of this family belong to the genus *Morus* L., adding a total of 150 species, among them, *Morus alba* L. . (Martins 2018).

It is a monoic or dioecious shrub or tree, with a height that varies from 3 to 10 meters. It has a gray or brown trunk and its branch is cylindrical and green. It has a white sap lactescent. Its stipple is green and elongated and its leaves are membranaceous, oval or elliptical, obtuse, or cordiform, with acute apex. The nervation of this species is brachydródoma with 2 basal pairs and up to 4 secondary pairs. Leaf margins can be serrated or whole, usually 2-6 lobed. Petioles are canalicular, with white or yellowish trichomes. The inflorescence of this plant is solitary; female flowers have a short stylus or do not. Infructescence is pendulous and its color varies from green to pink or almost black (Souza 2009).

Morus alba L. (Linnaeus 1753) is a plant from Asia, widely cultivated in countries like China and Japan, due to its use as food for the silkworm (*Bombyx mori*), in addition to its use in traditional Chinese medicine for acting as a hepatoprotective, hypotensive, antipyretic, analgesic and diuretic agent (Oliverira 2013; Santos 2015; Martins 2018).

It is a species that has sources of secondary metabolites that have biological and pharmacological activities, such as the presence of flavonoid compounds and anthocyanins (Piekarsk 2013). These fruits contain reserves of sugars and organic acids, and, according to studies, great genetic variability, giving the genus presentations of morphological changes according to the ecological conditions of cultivation (Kafkas 2006).

Experimental Section

The botanical material was collected in September 2016, at location 0º01'30.9 "S 51º10'18" W, in the municipality of Santana / AP. The mulberry leaves went through the drying process at room temperature. After dry and crushed, the yield was 484 g, which were macerated and rotated, obtaining 87.5 g of Extract Crude Hydroalcoholic (ECH).

Phytochemical Evaluation

The phytochemical study of the EBH of *M. alba* leaves was carried out using the methodology proposed by Barbosa (2004), where it is based on precipitation and color reactions.

Evaluation of Antioxidant Activity

Through the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, based on the electron transfer by antioxidant action, samples in triplicate of hydroalcoholic extract were evaluated based on the methodology proposed by Souza *et al.* (2007), and Lopes-Lutz *et al.* (2008). A methanolic solution of DPPH at a concentration of 40 µg / mL^{-1} was prepared and kept in a dark place. The EBH of *M. alba* leaves were diluted in methanol at concentrations of 0.25; 0.5; 0.75; 1; 2.5 and 5 $mg.mL^{-1}$. In test tubes, 2.7 mL of the DPPH solution and 0.3 mL of the plant extract solution were added. After a short period of time, sample readings were started.

Calculations for determining Antioxidant Activity were performed using the following equation:

$$\%AA = \frac{\text{AbsSample} - \text{AbsWhite} \times 100}{\text{Abscontrol}}$$

%AA – percentage of antioxidant activity
Abs_{Sample} – Sample absorbance
Abs_{White} – White absorbance
$Abs_{Control}$ – Control absorbance

Evaluation of Antimicrobial Activity

Strains of *Staphylococcus aureus* (ATCC 25922), Gram-positive bacteria, were used. From the culture of the strains, the bacteria were reactivated, kept in Muller-Hinton broth (CMH) and after solidification, a solution of the *M. alba* plant extract was impregnated on the surface and incubated for 18h at 37 ° C. incubation, microbial inhibition halos were observed.

For the Minimum Inhibitory Concentration (MIC) the extract was diluted in 4% DMSO. NaCl and *M. alba* extract solution were added to the wells of the plates, 50 µL of each. After a series of dilutions, the wells were filled with a distribution of 50 µL of suspensions containing *S. aureus*. Amoxicillin (50 $\mu L.mL^{-1}$) was used for the positive control. The experiment was carried out in triplicate and the plate was incubated for 24h at 37ºC.

RESULTS AND DISCUSSION

The hydroalcoholic extract of white mulberry leaves, from the proper phytochemical analysis procedures, showed positive reactions for reducing sugars, azulenes, derivatives of coumarin, and flavonoids, according to **Table 1**.

Secondary metabolites are substances of low molecular weight, usually of the complex structure, that have biological activities that are different from the primary metabolites. These substances arouse great interest, either by promoting biological activities to plants as a defense mechanism in response to the environment or by the pharmacological action they provide to human beings (Pereira; Cardoso 2012).

Among the secondary metabolites present in the hydroalcoholic extract of *M. alba*, we have reducing sugars, derived from aldose that have free carbonyl groups, which can reduce by the presence of free aldehydes or ketones. These sugars add flavor to the food and act as reducing agents in the body.

Azulenes have anti-inflammatory activity, usually resulting from the degradation of matricin, present in some types of extracts and essential oils (Simões *et al*. 2001).

Flavonoids are metabolites that promote direct actions in the body related to the sequestration of free radicals by transferring hydrogen atoms.

As for coumarin derivatives, they originate from pyrone, coumarins are benzo-derived heterosides, and may have a natural or synthetic origin (Gama 2011). They are well distributed among plants, fungi, and bactéria (Simões *et al*. 2001). They are substances that have great potential for the synthesis of drugs because they contain important biological actions.

A drug derived from coumarins and that has great pharmaceutical importance is dicumarol, which acts as an antagonist to Vitamin K, interfering in its metabolism and inhibiting the hepatic synthesis of factors that depend on this vitamin to promote coagulant action (Souza 2005).

Antioxidant Evaluation

DPPH is a free radical used to assess the antioxidant capacity of phenolic compounds by transferring H atoms to radicals. The hydroalcoholic extract of *M. alba* showed an increase in antioxidant activity according to the increase in concentration, as shown in **Table 2**, reaching 97.65% of antioxidant activity in the highest concentration.

The antioxidant action of *M. alba* leaf extract is closely related to the presence of secondary metabolites such as flavonoids, substances capable of promoting the action of interrupting the chain of free radicals during the beginning of the oxidative process through primary antioxidant substances (Melo 2014).

Other secondary metabolites determining the antioxidant action present in the extract of *M. alba* are coumarins. Studies report the ability of these substances to prevent the formation of reactive oxygen species and, consequently, oxidative stress (Corrêa 2015).

A free radical is characterized by an organic or inorganic molecule, which contains paired electrons and which have an independent existence. Free radicals are produced through physiological processes, generated in the mitochondria or the membrane of your cellular target (Bianchi 1999). However, eventually, there is an increase in the production of reactive oxygen species, causing oxidative stress. These substances can trigger damage to the body, such as the lipoperoxidation of unsaturated lipids from cell membranes (Pereira; Cardoso 2012).

Oxidative lesions promoted by free radicals in cells and tissues are related to the development of diseases, even degenerative ones, such as heart diseases, lung diseases, and atherosclerosis, in addition to the damage caused to DNA through enzymatic actions, playing an important role in the process of carcinogenesis and mutagenesis (Bianchi 1999).

Antioxidants are endogenous or exogenous substances capable of delaying or preventing oxidative damage, even though they are in lower concentrations than the oxidizing agent. They can act in several stages of the oxidative process through different mechanisms, being classified into primary and secondary antioxidants. Primary antioxidants inhibit or delay oxidation by donating hydrogen atoms, turning free radicals into stable molecules. Secondary antioxidants act in several ways, including the bonding of metal ions, which alter the valence; inactivation of reactive oxygen species; conversion of peroxides into non-root species, and radiation absorption (Silva 2010).

Microbiological Evaluation

The results obtained from the microbiological tests showed that *Staphylococcus aureus* bacteria are susceptible to the hydroalcoholic extract of *M. alba*, presenting an antimicrobial potential for bacteriostatic characteristics, that is, limiting bacterial growth. According to **Fig. 1**, the concentration of 100 mg/ml of the extract of *M. alba* was more effective about antimicrobial activity. Through phytochemical screening, it was possible to observe the presence of secondary metabolites relevant to the promotion of antimicrobial activity, such as flavonoid compounds and coumarin derivatives.

Antimicrobial agents isolated from plants can act as regulatory compounds for intermediate metabolism, being able to activate or block enzymatic reactions, directly affecting them, whether at the ribosomal or nuclear level or even from changes in bacterial cell membranes (Gonçalves 2007).

These secondary metabolites, in addition to assisting in the development and growth of the plant, some classes have characteristic biological activities, which have antioxidant, anti-inflammatory, and antimicrobial properties (Simões *et al*. 2001). Variations in the structures of Gram-positive and Gram-negative bacteria can cause differentiated damage when the bacteria subjected to antimicrobial compounds in their permeability properties of cell membranes and surface components. According to studies, the antimicrobial action of flavonoids can form complexes between soluble proteins and the bacterial cell wall (Johann 2003).

There are reports of the efficient action of pure coumarins as an antimicrobial agent against Gram-positive, gram-negative, and fungi; as well as promising studies regarding antiprotozoal activity (Domingo 2003). Some classes of coumarin antibiotics act directly on bacterial DNA gyrase, inhibiting the production of ATPase. Consequently, some classes are active against *Staphylococcus aureus* (Souza 2005).

CONCLUSION

Studies obtained from research and analysis of medicinal plants that have substances for the development of potential phytopharmaceuticals, become essential for scientific knowledge. *Morus alba* has secondary metabolites efficient in promoting antioxidant and antimicrobial activities, reaching satisfactory levels of antioxidant action, offering natural and alternative methods for the prevention of certain diseases, such as heart disease, atherosclerosis and lung diseases.

Due to the indiscriminate use of antimicrobials, bacterial strains become increasingly resistant to these drugs, thus, the results obtained to expand the knowledge regarding the antibacterial activity in extracts of species such as *Morus alba*, highlighting their effectiveness.

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