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CARDIOPROTECTIVE ACTIVITY ASSOCIATED WITH THE USE OF THE GUAZUMA ULMIFOLIA LAM. AN INTEGRATIVE REVIEW OF THE LITERATURE

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ABSTRACT

Comorbidities, particularly those related to the cardiovascular system, are prevalent in today's lifestyle, contributing significantly to morbidity and mortality rates according to the World Health Organization. Obesity and sedentary habits further exacerbate cardiovascular risks, often demanding multidrug therapies. Herbal medicine offers popular alternatives to reduce drug reliance, with plants like Guazuma ulmifolia playing a significant role due to its geographical prevalence and the presence of beneficial compounds such as proanthocyanidins, epicatechins, and flavonoids. This review aims to highlight G. ulmifolia's positive impact on cardiovascular health based on existing evidence. An integrative literature review was conducted using SCOPUS, PUBMED, and WEB OF SCIENCE databases with specified descriptors like "Phytotherapy", "Guazuma ulmifolia" and "Mutamba". Studies indicate that G. ulmifolia exhibits anti-inflammatory, hypoglycemic, vasodilatory, antioxidant, and cardiotonic properties attributed to its phenolic compounds. Ultimately, the cardioprotective potential of G. ulmifolia suggests its promising role as an adjunct therapy alongside conventional treatments, although further research is warranted to enhance the understanding of its therapeutic mechanisms.

Keywords: Medicinal Plants. Cardiotonic Agents. Flavonoids. Metabolic Syndrome.

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INTRODUCTION

The advent of industrial development within society has profoundly altered both the societal lifestyle and the dietary habits of its population, which is mostly unhealthy. In this regard, cardiovascular disease notifications have increased and have become one of the leading public health issues (Silva, 2013)[1]. According to the World Health Organization (WHO)[2], cardiovascular diseases (CVD) are the leading cause of death in the world and responsible for 31% of global deaths; arterial hypertension, one of the main risk factors for CVD development, affects approximately 25% of Brazilian population, on the report of official data of Pesquisa Nacional de Saúde (PNS)[3], held in 2019.

Furthermore, obesity and a sedentary lifestyle are risk factors that contribute to the increase in the incidence of CVD in the country. Based on the research Vigitel from the Brazilian Ministry of Health (MS) held in 2019, approximately 60% of the Brazilian population is overweight. Around 37% have a sedentary lifestyle, which shows the importance of public policies and preventive measures to fight against risk factors and prevent CVD development in Brazil. (MS, 2020)[4]

Cardiovascular diseases have well-elucidated modifiable risk factors, which the majority associate with a degenerative way of life. On the other hand, other conditions can trigger heart issues, such as comorbidities related to metabolic syndrome (Duque *et al.*, 2018)[5]. It stands out that the majority of patients with arterial hypertension need two or more antihypertensive drugs from different therapeutic classes to achieve ideal blood pressure values since only one-third of them achieve this goal with only one medication (Barroso *et al.*, 2020)[6].

Alternative therapies appear as workable resources for treating many chronic illnesses. In that respect, many medicine plants have been used as an adjunct to traditional protocols, reducing the adverse effects of drug treatments that lead to oxidative stress. Otherwise, the influence of nature on human life is unquestionable, especially in health, be it directly or indirectly (Silva, 2013).[1]

Medicine plants, constituents of biodiversity, are used in traditional communities as homemade remedies and considered essential raw materials for the manufacturing of herbal medicine, among other drugs. The use of vegetal material aims to be a therapeutic resource and prevention that seeks to take advantage of the benefits offered by the plants without isolating the active ingredients due to what is done by the pharmaceutical industry (Leão *et al.*, 2007).[7]

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Facing the perspective of alternative and complementary therapy, *Guazuma ulmifolia*, native of tropical America, also known as Mutamba, Mutamba-preta, Guaxima-macho, Marolinho ou Pojó, is an example of a natural resource much used in popular medicine. This plant has a broader geographic distribution in America. In Brazil, it exists in all regions of the country, mainly in the north and central-west regions (Carvalho, 2007)[8].

The use of plants in medicinal treatments raises important ethical questions, particularly when it comes to the sustainability of natural resources and respect for local knowledge. Plants like *Guazuma ulmifolia* have long been utilized by traditional communities, and it is crucial to acknowledge their contributions to modern medicine (Carvalho,2007)[8]. Exploiting these resources without proper recognition or fair compensation to the original knowledge holders can lead to issues of biopiracy, where the benefits of plant-based discoveries disproportionately favor pharmaceutical companies rather than the communities that cultivated this knowledge. Thus, it is essential to promote ethical guidelines that protect biodiversity and ensure that the use of medicinal plants respects intellectual property rights and the principles of fairness. (Khakurel *et al*., 2022)[9].

Moreover, the conservation of medicinal plants is a growing concern. As the demand for natural remedies increases, the overharvesting of plants like *Guazuma ulmifolia* could pose a threat to ecosystems and biodiversity. Ethical practices in harvesting and cultivation must prioritize sustainability to prevent the depletion of natural resources. Furthermore, research involving medicinal plants should be conducted with transparency and adhere to environmental protection regulations. This ensures that the benefits of such plants are accessible to future generations while maintaining ecological balance and respecting the cultural and environmental significance of the species. (Khakurel *et al*., 2022)[9].

The *G. ulmifolia* is an evergreen tree with a straight to tortuous trunk, very branched, and it can reach 30 meters in length. Its bark is rough, greyish to dark coffee, lengthwise chapped, and it detaches easily in the form of plaques; the older the plant, the more evident its characteristics are. Its leaves are simple, oval and jagged. It shows small flowers, yellowed and slightly dry and verrucous, stiff. Its seeds are oval, brown to black, and hard (Pereira *et al*., 2019).[10]

G. ulmifolia is popularly used by latin-americans from the decoction of the bark's trunk, fruits, and leaves to treat gastrointestinal and cardiovascular disturbs, and its use can be proven by studies *in vitro* e *in vitro* (Martins, 2017)[11]. According to Cunha (2019)[12], this species has been used in alternative therapies due to its anti-microbial, anti-diarrhea, anti-

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oxidative, anti-inflammatory, anti-protozoal, anti-hypercholesterolemic, hypotensive, vasodilator and cardioprotective.

The existence of phenolic compounds such as proanthocyanidins, tannins, aglycones, saponins, mucilages, alkaloids, triterpenes, steroids, and glycosylated flavonoids foster the therapeutic potential of the plant. In these terms, it is valid to mark that in the bark of the trunk, there are more proanthocyanidins, glycosylated flavonoids, and phenolic acids as secondary metabolites, studied as fosterers of the process of protection, mainly what is referred to as cardiovascular activity. (Martins, 2017)[11]

In addition, Mafra et al. (2019)[12], after conducting the toxicity test, noted that mutamba extract does not have toxic potential until the dosage of two thousand milligrams per kilogram (2g/kg); thus, it can be pharmacologically explored with a safety margin.

Therefore, it becomes evident that the focus of this review is to assess and elucidate from the literature the active compounds in *G. ulmifolia* that can impact effectively in cardiovascular system disorders.

METHODS

This study is an integrative literature review carried out in databases SCOPUS, PUBMED, and WEB OF SCIENCE. To refine the searches, descriptors were listed as: “Phytotherapy”, “Guazuma ulmifolia”, and “Mutamba”. The inclusion criteria for selecting articles are related to the date of publication and the impact of literary productions, with a preference for using data collected in the last five years. Despite the fact that many significant articles, albeit not so current, were also considered. In addition, original articles in English and Portuguese were listed. As exclusion criteria, articles that did not fit the descriptors and were not in Portuguese or English were considered.

Based on data collection requirements, 75 references were obtained, categorized by type of publication, and which specifically elucidated the objectives of this study. As a result, after applying the exclusion criteria, 28 articles remained.

RESULTS AND INTERPRETATION

Medicine plants have had wide usage since the beginning, having a significant role in therapies and interventions for many pathologies. This situation occurs due to the existence of metabolites that enable their usage since they act to reduce adverse effects provoked by synthetic drugs without decreasing the therapeutic impact (Santos *et al.*, 2021)[13].

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From the studies carried out, it was discovered that there was a significant contribution of *G. ulmifolia*, above all, when applied to cardioprotective effects in the organism. Even though most of the published research did not directly address the cardioprotective effect of *Guazuma ulmifolia*, there is a demonstration of the expression of secondary metabolites that wisely exercise positive effects on health (Cunha *et al*., 2019)[14].

Among the main metabolites found phenolic compounds, as flavonoids, proanthocyanidins, epicatechins, and tannins. They show a large spectrum of organic activity, being them anti-microbial, anti-diarrhea, anti-oxidative, anti-inflammatory, anti-protozoal, anti-hypercholesterolemic, vasodilator, and cardioprotective (Tanase *et al*., 2019)[15].

Table 1: Compounds identified in *Guazuma ulmifolia* Lam. and their respective actions

FLAVONOIDS	
METABOLITES	ACTION
Proanthocyanidin	- Inhibit binding of angiotensin - II to the human AT1 receptor - Anti-inflammatory action, by the inhibition of STAT 1-DNA, which is responsible for activating the transcription nuclear mechanism - Oligomeric proanthocyanidins have activity on the circulatory system, which is based on the dilatation of coronary walls and positive inotropic effect - Flavan-3-ols, proanthocyanidin, and hydrolyzable tannin can catch oxygen-free radicals responsible for the inflammatory process.
Catenins	- Anti-inflammatory action, by inhibiting the STAT 1-DNA, is responsible for activating the nuclear transcription mechanism.
Epigallocatechin	- Anti-inflammatory action, for inhibiting the SAT 1-DNA, is responsible for activating the nuclear transcription mechanism.
Quercetins	- . Antiínflammatory action by inhibiting Interleukins-6 (IL6) and C-reactive protein (CRP) - The anti-oxidative action helps neutralize free radicals, protecting oxidative stress cells and preventing cellular damage.
Luteolin	- Anti-oxidative action, anti-tumor action, and anti-inflammatory action; - Cell proliferation inhibitor; - Cardiovascular protection; - Neuroinflammation modulator.
Procyanidins	- Inhibition activity of intestinal hydrochloric secretion
OTHER COMPOUNDS	
Tannins	- Flavan-3-ols, proanthocyanidin, and hydrolyzable tannin can catch oxygen-free radicals responsible for the inflammatory process.

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	- Tannins and phenolic compounds have been widely recognized for high antibiotic potential;
β-sitosterol	- Cholesterol reduction; - Anti-inflammatory effect; - Antioxidant activity; - Effects on immune function; - Anticancer potential;
Saponins	- Diuretic activity, blood purifying, and expectorant activity.
Terpenes	- Anti-inflammatory effect.

Source: Own elaboration.

VASODILATOR ACTION

Among the compounds found in mutamba extract, proanthocyanidin is a crucial vasodilator. For example, in cases of increased blood pressure caused by the Renin-Angiotensin-Aldosterone System (RAAS), angiotensin II binds to the human AT1 receptor. In this sense, this binding promotes vasoconstriction, activation of the sympathetic nervous system (SNS), increased aldosterone, increased ADH, cell proliferation, fibrosis, and oxidative stress (Sanjuliani, 2011)[16].

According to Caetano (2023)[17], the existence of proanthocyanidins results in an anti-inflammatory process and determines a significant increase in nitric oxide production and inhibition of lipid peroxidation.

[3H]Angiotensin II acts as a potent vasoconstrictor and stimulates aldosterone in case of hypovolemia. From proanthocyanidin B action, there is an inhibition of binding between [3H]angiotensin II and human AT1 by an antagonist mechanism, resulting in normotension (Caballero-George, 2002)[18].

Phenolic compounds found in the extract of *G. ulmifolia*, as oligomeric proanthocyanidins, have hypotensive properties through vasorelaxant effect and negative chronotropic effect observed specifically in hypertensive cases. Thus, it is observed that the decreasing cardiac frequency is due to the inhibition of cardiac adrenergic receptor alfa-1 (Magos *et. al.*, 2008)[19].

ANTI-OXIDATIVE ACTION AND CARDIOPROTECTIVE EFFECT

During energy formation in the mitochondrial respiratory chain, it built Reactive-Oxigen Species (ROS). In specific quantities, they regulate the cell cycle in the mechanism of gene expression and apoptosis. In the presence of any disbalance or excess free

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radicals, it occurs an interaction with other molecules that can provoke damage to health. Due to this disturbance between the capacity to neutralize free radicals and excess production, hence, oxidative stress (Santos, 2017)[20].

Oxidative stress fosters significantly in cell structure, peptide functions, and nucleic acids, being involved in cardiovascular diseases' etiology for damaging heart tissue. Furthermore, lipid peroxidation, anti-oxidative reduction, and activation of apoptotic pathways provoke irreversible functional loss for heart cells (Santos, 2017)[20].

In chromatographic tests, compounds such as tannins and anthocyanidins have anti-oxidative action. Being them, the polyphenols present in *G. ulmifolia* are responsible for anti-oxidative function. The hydroxyl group empowers these compounds to catch free radicals and turn them into intermediary stable substances to carry out their action (Tanase *et al.*, 2019)[14]. The flavonoids, also present in *G. ulmifolia*, are abundant dietary polyphenols, being more connected to sugar (glycosides). In addition, it was discovered that flavonoids and their metabolites act as signaling molecules by actions on protein kinase and lipid kinase signaling pathways (Kasote *et al.*, 2015)[21].

The cardioprotective effect searched in *G. ulmifolia* extract has the mechanism of action to decrease possible cardiotoxic effects as well as the prevention of the production of malonic dialdehyde (MDA) in heart tissue, a biomarker of oxidative stress that constitutes the final product of lipid peroxidation. Furthermore, there is enzymatic action as procyanidin and catechin that act in peroxidation reduction. *G. ulmifolia* is capable of suppressing oxidative stress through the action of its phytochemicals compounds that operate in the direct elimination of Reactive Oxygen Species (ROS) and the inhibition of processes such as peroxidation in erythrocytes and myocytes (Santos, 2017)[20].

In addition, Da Silva *et al.* (2021)[22] describes in depth an experimental process involving the preparation of the extract of *G. ulmifolia's* bark, the phytochemical analysis of the extract, and the animal tests promotion to evaluate herbal medicine potentials, standing-out cardioprotective action. The execution of the tests on rats results in the suppression of oxidative stress, cleaning of free radicals, inhibition of oxidative hemolysis, and reduction of MDA production in cardiac tissues, among other beneficial effects of the extract.

Jessica Maurino dos Santos (2019)[20] shows that in the ethanolic extract of *G. ulmifolia*, due to the existence of flavonoids proanthocyanidins, catechins, quercetins, and luteolin, it presented an oxidative power by the suppression of ROS's synthesis. Still along

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the same lines, it's important to mention that Oliveira (2012)[23] quotes that flavonoids, abundant metabolites in *G. ulmifolia* donate oxygen atoms to peroxyl radicals, playing an essential role in significantly reducing superoxide ions and hydroxyl radicals. Otherwise, they effectively participate in the chelation of metals in ROS-producing reactions, which triggers a significant cardioprotection effect.

HYPOGLYCEMIC ACTION

Upon consumption of food and carbohydrates, glucose enters the cell through the GLUT-4 transporter, initiating glycolysis and pyruvate formation. As a result of this process, the compound enters the mitochondria and participates in the Krebs cycle, leading to the formation of intermediary citrate substances. These substances serve as precursors for lipogenesis, ultimately resulting in the formation of fatty acids that are deposited into the cell, awaiting mobilization to meet energetic needs (Souza, 2011)[24].

About Hypoglycemic effects, a study held by Adnyana *et al.* (2013)[25] showed that the ethanolic extract of mutamba could reduce glucose due to the stimulation of insulin secretion by pancreatic beta cells and increase the sensibility of insulin receptors. In contrast, Alonso-Castro and Salazar-Olivoy (2008)[26] report anti-diabetic effects owing to the capitation of glucose into adipocytes, both responsive and resistant to insulin effects, without affecting the development of adipocyte tissue. The inducing potential of glucose uptake in insulin-resistant adipocytes, in addition to the lack of pro-adipogenic or anti-adipogenic effects, suggests that *G. ulmifolia* can be very useful in the treatment of type II diabetes mellitus, which is a significant risk factor in the onset of heart disease.

ANTI-INFLAMMATORY ACTION

Inflammation is a natural organism reaction due to tissue injuries from traumas, infections, and immunologic reactions. Such a mechanism is mediated by cells, blood vessels, cytokines, and chemokines that act as mediators. A vital precursor compound of this process is the arachidonic acid cascade, which stimulates the action of prostaglandins, leukotrienes, and thromboxanes. Other inflammatory mediators, such as interleukins, tumor necrosis factor-alpha (TNF-α), and nitric oxide act effectively in the inflammatory process. The existing metabolites in *G. ulmifolia* have shown promising results in modulating this process (Etienne, 2021)[27].

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Studies demonstrate that polyphenols reduce lipid peroxidation and DNA damage, in addition to acting in the induction of the blocking mechanism for the high production of tumor necrosis factor, promoting an anti-inflammatory effect. In inflamed tissues, an increase in the synthesis of nitric oxide (NO) was observed. When inflamed tissues are subjected to contact with quercetin, metabolites present in G. ulmifolia extract undergo a significant reduction in the synthesis of nitrogen monoxide by inhibiting eNOX (nitric oxide synthase) (Tanase *et. al.*, 2019)[15].

According to M. Maldini *et al.* (2012)[28], the methanolic extract fraction of mutamba bark rich in proanthocyanidins, epigallocatechin, and epicatechin has anti-inflammatory action due to the inhibition of STAT 1-DNA, responsible for activating the nuclear transcription mechanism. In this context, according to Pashkow (2011)[29], the inflammatory process involves a series of events and molecules, including the nuclear factor NF-kappa-B, Nitric Oxide Synthetase (eNOX), Tumor Necrosis Factor Alpha type (TNF-α) and Cyclooxygenase 2 (COX-2), which together lead to inflammation. Therefore, it can be seen that the metabolites present in the extract will act to block the activation of these factors; consequently, the inflammatory condition will not occur as it does not allow the synthesis of free radicals.

In short, *G. ulmifolia* has a vasodilatory, antioxidant, hypoglycemic, and anti-inflammatory action, demonstrating significant pharmacological potential in the regulation and maintenance of homeostasis, thus enabling its wide use in alternative medicine, as explained.

FINAL CONSIDERATIONS

In front of the shown studies, it is clear the non-toxicity of *Guazuma ulmifolia* suggests the possibility of enlargement of the usage of the plant as a cardioprotector agent, in addition to the usage of this input to other purposes in health, as already happens in popular medicine. The connection between the non-toxic and the expression of beneficial mechanisms to health amplifies the pharmacological potential of mutamba.

Therefore, mutamba owns into its composition alkaloids, tannins, flavonoids, cardiac glycosides, steroids, and other components that mediate protective activities, standing out with cardioprotective potential. A beneficial and efficient exploration of the plant for health promotion is necessary to foster a more extensive scientific investigation of this input once it already has shown a valuable healing and preventive potential for various diseases. Thus, it

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could yet be discovered new active principles and new pharmacological activities of known substances.

In addition, it is essential to carry out consecutive temporary assessments to understand the phenolic patterns of the plant better once the seasonality could interfere with the expression of different phytochemicals compounds of the plant. So, it would be possible to improve quality control of *Guazuma ulmifolia* to ensure extensive security of the usage of this resource.

In summary, the results involving the cardioprotective effect of *G. ulmifolia* indicate a high usage potential as a therapeutic resource when associated with conventional therapies. However, there is a necessity to launch more studies to deepen the knowledge about this plant.

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