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THERAPEUTICS PERSPECTIVES OF THE *Hancornia speciosa* GOMES: BIOACTIVE COMPOUNDS IN THE FRUIT, LEAVES, BARK AND LATEX

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ABSTRACT

Introduction: *Hancornia speciosa* Gomes is a plant used in traditional Brazilian medicine. Its therapeutic activity can be explained by the presence of secondary metabolites. It is found in biomes such as the Amazon, Brazilian semiarid (caatinga), Atlantic forest and cerrado. The objective of this study was to review the literature, compiling information and identifying factors that influence its therapeutic activity as well as arousing interest in new studies. **Methodology:** The search included PubMed, Web of Science, Science Direct, Scielo, Medline and Google Scholar databases using the keywords "*Hancornia speciosa* Gomes", "Natural Polymers", "Mangaba", "Magabeira", "Chlorogenic acid", "Rutin", "Naringerin", "Bornesitol", "Hancornia Latex", "Phytotherapy", "Ethnopharmacology", "Medicinal plants" and the relationship between them. The search was complemented by reading the referenced articles and updated until May 2022. **Results:** Due to its rich content of bioactive compounds, it may be a promising choice for nutraceuticals and therapeutics with anti-inflammatory, antibacterial, antihypertensive, gastroprotective, hepatoprotective, dermo protective, osteogenic and angiogenic properties. **Conclusion:** From a scientific point of view, it is necessary to standardize dosages, evaluate the pharmacodynamics, pharmacokinetics and toxicology, especially regarding the use of latex with the potential presence of pathogens in its composition. Randomized clinical studies based on the knowledge and popular use of this plant should be carried out after preclinical studies to prove its efficacy and safety.

Keywords: *Hancornia speciosa;* Mangaba; Ethnopharmacology; Plants Medicinal; Phytotherapy.

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1 INTRODUCTION

Medicinal plants are used all over the world and they need to be safe, with expected pharmacological results confirmed, acceptable levels of microbial contamination and no spoilage or pathogenic microorganisms (DIAS, PEREIRA, ESTEVINHO, 2012).

Several plants are used in the Brazilian traditional medicine. *Hancornia speciosa* Gomes (HS) is a fruit tree of the Apocynaceae family that produces a fruit known as "mangaba". It is found in the Amazon, Brazilian semiarid (caatinga), Atlantic forest and Brazilian savannah (cerrado) biomes.

The therapeutic potential of its parts (fruits, leaves, bark and latex) has been investigated (DOS SANTOS *et al.*, 2018) and could be found in studies identifying antibacterial (BARBOSA *et al.*, 2019), antidiabetic (PEREIRA *et al.*, 2015), antihypertensive (MOREIRA *et al*., 2020), antioxidant, antimutagenic, anti-inflammatory, antiobesity, antihyperglycemic properties. It has also been described as adjunctive treatment for Alzheimer's and Parkinson's disease (DOS SANTOS *et al.*, 2018). These therapeutic activities can be explained by the presence of phenolic compounds, tannins, alkaloids, triterpenes and steroids, lipophilic compounds, lignin, starch and calcium oxalate crystals (CAMPOS *et al.*, 2021).

In order to expand the knowledge about this Brazilian plant, the objective of this study was to review the literature on HS, compiling information and identifying possible factors influencing its therapeutic activity.

2 METHODOLOGY

Narrative review with scientific productions indexed in the following electronic databases: PubMed, Web of Science, Science Direct, Scielo, Medline and Google Scholar databases. The articles selection was based on the abstracts analysis where there was a relationship between the plant and the pharmacological and/or nutraceutical activity. The descriptors were "*Hancornia speciosa* Gomes", "Natural Polymers", "Mangaba", "Magabeira", "Chlorogenic acid", "Rutin", "Naringerin", "Bornesitol", "Hancornia Latex", "Phytotherapy", "Ethnopharmacology", "Medicinal plants", and the relationship between them. The research was complemented by an electronic search of the references cited in the selected articles. The oldest article included, date from 1999. The survey was updated until May 2022.

3 RESULTS AND DISCUSSION

3.1 *Hancornia speciosa* Gomes

Apocynaceae is a family that includes from 3,700 to 5,100 species distributed in several places in the world, but mainly in tropical and subtropical regions, with approximately 90 genera and 850 species of this family in Brazil. Within this large botanical family is the monotypic genus Hancornia with the species *Hancornia speciosa* Gomes (BASTOS *et al.*, 2017), popularly known as "mangabeira", a fruit tree native to the Brazilian flora (DOS SANTOS *et al.*, 2018). (Fig.1)

Fig.1: *Hancornia speciosa* Gomes - Tree from Brazilian savannah (cerrado). **Source:** Pictures kindly provided by Prof. Eros Bittencourt Shigeto and prepared by Victor Augusto Benedicto dos Santos

Its height varies between 5 to 7 m (COUTINHO & LOUZADA, 2018), its fruit called "mangaba" is very popular for consumption, and its latex, bark and leaves have been used to treat Alzheimer's disease, hyperlipidemia, obesity, diabetes, dermatosis, diarrhea, gastritis, ulcer, indigestion, hypertension and diseases of the genitourinary tract (CAMPOS *et al.*, 2021). The leaves extract as well as the stem, are also used in the cosmetic industry due to the presence of some secondary metabolites, important for this product line (CHAVES *et al.*, 2020).

The fruit - Mangaba

The mangaba is yellow, with small red spots, has a bittersweet pulp that represents 77% of the fruit's composition. It is part of the local populations diet being considered a good source of vitamins and minerals. The food industry uses it mainly as juices, sweets and ice-cream production, playing an important role in the local economy (REIS & SCHMIELE, 2019). (Fig.2A)

The high iron content characterizes it as one of the richest fruits in this mineral, being also a great vitamin C and phenolic compounds (phenolic acids and flavonoids) source, which can help in the elimination of free radicals. The main phenolic and organic compounds described in the mangaba pulp composition are L-bornesitol, quinic acid, ascorbic acid, chlorogenic acid, isochlorogenic acid, 3-feruloylquinic acid, rutin, 5-feruloylquinic acid, quercetin-3-O-hexoside, kaempferol-rutinoside, kaempferohexoside, isorhamnetin-3-O-rutinoside and quercetin, with rutin and chlorogenic acid described as having the highest bioactivity (DE OLIVEIRA YAMASHITA *et al.*, 2020).

The fruit extract from several Brazilian regions were previously analyzed by high performance

liquid chromatography, identifying chlorogenic acid (93.71-131.66 mg.100 g $^{-1}$), ferulic acid (0.85-2.27 mg.100 g $^{-1}$) and rutin (238.59-442.94 mg.100 g $^{-1}$). The fruit extracts from Bahia and Sergipe regions, are the ones presenting the highest concentration of the rutin (436.78 and 442.94 mg.100 g^{-1}). This information is important for future studies with these compounds in pharmacological applications (SANTOS *et al.*, 2021).

Leaves of "mangabeira"

The mangabeira's leaves are used for medicinal purposes and they seem microbiologically safety. Carotenoids and polyunsaturated fatty acids were identified in an ethanolic extract and showed antioxidant, antimutagenic, anti-inflammatory, anti-Alzheimer's disease, anti-Parkinson's disease, antiobesity, and anti-hyperglycemic activities (DOS SANTOS *et al*., 2018). (Fig.2B)

Regarding biological activities, antibacterial, antidiabetic, antihypertensive and cytotoxic effects were demonstrated. Rutin was reported having antihypertensive effect (CAMPOS *et al.*, 2021).

Other phenolic compounds have also been identified, including caffeic acid, protocatechuic acid isomers, epicatechin, quercetin isomers, type B and type C procyanidins, coumaroylquinic acid isomers, phlorizin, phloretin, eriodictol, luteolin and apigenin. Natural extracts and phenolic derivatives with pharmacological potential can serve as a safe and economical treatment strategy, and a possible alternative to synthetic drugs (BASTOS *et al.*, 2017).

Secondary metabolites found in the leaves and also in the stem, such as saponins, tannins and the flavonoids themselves, are also used in cosmetology. Saponins are used in shampoo and soap formulations for their foaming and detergent activity. Tannins and flavonoids can be incorporated into creams, gels and serums for antioxidant, depigmenting and sun protection purposes (CHAVES *et al.*, 2020).

Bark of "mangabeira":

The hydroethanolic extract of the bark was able to protect the gastric mucosa against ulcers and exert an antioxidant effect (MORAES *et al.*, 2008; DE OLIVEIRA YAMASHITA *et al*., 2020).(Fig.2C)

In addition, hexane and methanolic extracts showed antimicrobial effects against some bacteria, when used as a tea formulation in folk medicine, especially against *S. aureus* and *E. coli* (CORDEIRO *et al.*, 2019).

That is a diversity of endophytic fungi in the HS bark, and microorganisms are important promising targets for bioactive compounds with antimicrobial potential. The plants cultivation for production of bioactive compounds is an attractive target for studies optimizing their chemical characterization. These compounds can be used directly or as a basis for the synthesis of new antimicrobial agents (CHAGAS *et al.*, 2017).

Latex of "mangabeira":

Laticifers are tube-like structures and can be throughout the body of the plant, producing and storing latex, a milky fluid, which is released when the laticifers rupture, usually caused by physical damage to the stem (WAROWICKA, NAWROT, GOŹDZICKA-JÓZEFIAK, 2020). (Fig.2D)

Fig.2: A, The fruit - Mangaba; B, Leaves of "mangabeira"; C, Trunk - Bark of "mangabeira"; D, Latex of "mangabeira".
Source: Pictures kindly provided by Prof. Eros Bittencourt Shigeto and prepared by Victor Augusto Benedicto dos Santos

The preformed compounds, in the latex, such as peptidases, chitinases and chitin-binding proteins, play important defensive roles against microbes and/or insects, also building a front line against herbivores. Many proteins and secondary metabolites are synthesized and stored in laticifers, and recent evidence suggests that independent clusters of laticifers can arise in different organs and tissues in the same plant, exhibiting different chemical and biochemical contents. These compounds, including proteomes and secondary metabolites, are also distinct between taxonomically related species with similar metabolisms (RAMOS *et al.*, 2019).

The literature strongly suggests that latex is an adaptive response to environmental factors such as herbivory, a biotic stress. It was also suggested that the latex would be able to affect prokaryotic and eukaryotic organisms, requiring further studies to explain the action mechanisms of plant exudates, as well as the secondary metabolites interactions. As the function of latex would be plant defense, it would be a valuable resource as an alternative source of bioactive metabolites. Given the scarcity of active molecules against various microorganisms, the combination of these metabolites could be an alternative for new drugs (ABARCA, KLINKHAMER, CHOI, 2019).

HS latex leaks from the bark when attacked, however, as the bark is thick and the number of lactiferous vessels is greater in the innermost region, the bleeding using superficial cuts, as the technique for *Hevea brasiliensis*, is not efficient. Another observation is that with increasing environmental temperature, latex production is higher however, at the time of fruiting it is significantly lower. This happen probably because the plant would be using a fraction of secondary metabolites for fruit formation, generating a lower availability of these metabolites to latex formation (ARRUDA *et al.*, 2016).

The latex has, in addition, biotechnological potential for new drugs development, but even in natura, it has been used to prevent or cure gastric ulcers, skin wounds, tuberculosis, diabetes, hypertension. Reports have also suggested a latex activity in bone regeneration, in promoting angiogenesis, as an anti-inflammatory, antimicrobial and antifungal agent (PEGORIN *et al.,* 2021), which has led to new preclinical studies, still in progress, with the use of compounds from HS latex *in vivo.* (Fig.3 A, B, C)

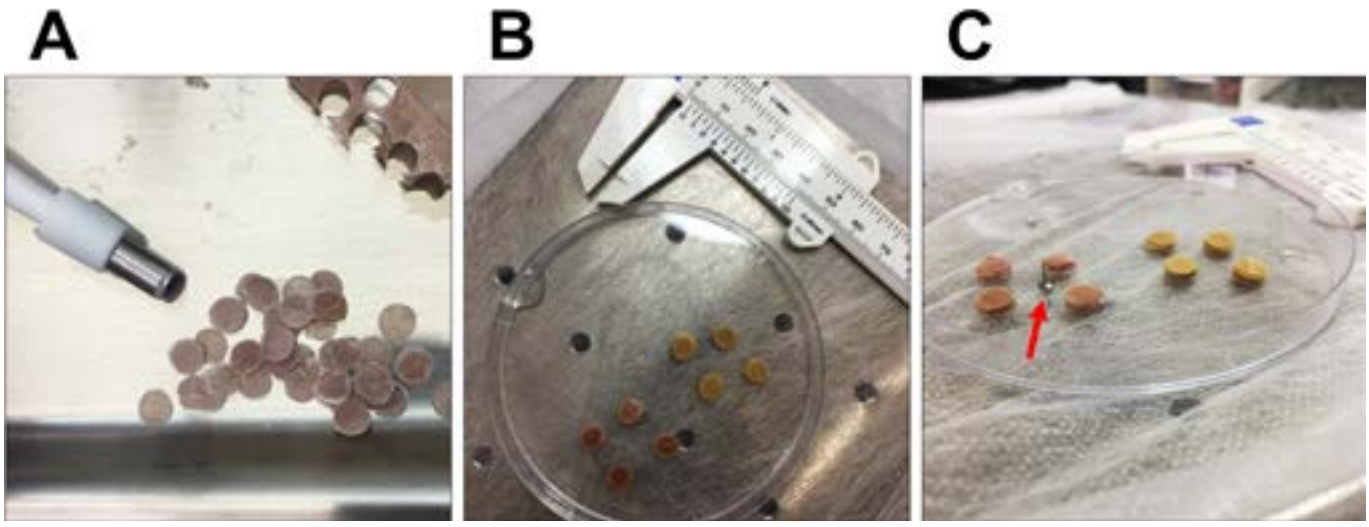

Fig.3 A,B,C: 5 X 0.6 mm discs, prepared with HS latex associated with other compounds (red arrow shows a screw used to fix the discs "*in vivo"*).
Source: Pictures provided by Dr Maria Cristina Pedrazini and prepared by Victor Augusto Benedicto dos Santos.

Regarding the origin of latex in rubber-producing laticiferous plants such as HS, there is a polyphase colloidal system involved. The dispersed phase is made up of rubber micelles and non-rubber vacuolar components and the dispersive medium is made up of an aqueous serum. For some researchers, latex from the same species presents qualitatively the same constituents, but there may be quantitative changes depending on environmental factors and phenological events. Water and soil nutrients *i.e.*, raw sap, are transported by the xylem, a living tissue of vascular plants present in the stem and leaves. After photosynthesis, the main constituent necessary for the plant's metabolic activities is formed, glucides or sucrose. Sucrose is carried by the phloem, another vascular living tissue responsible for carrying the soluble organic compounds produced during photosynthesis known as photosynthates, to the laticifer cells where latex is produced. The latex would be composed of isoprene units linked together forming polyisoprene (the rubber).Three basic stages have been established for the formation of latex: from sucrose, the formation of acetyl coenzyme A (acetyl-CoA) occurs, which is then converted into isopentenyl pyrophosphate (IPP) via mevalomic acid. The IPP is carried by the sap through the phloem to the lactiferous cells, where a special inner lining epithelium synthesizes cis-1,4 polysoprene (the latex). It is contained in tubes or in isolated cells known as lactiferous systems distributed throughout the cortex of the plant. Mangabeira latex has a milky appearance, a slightly pinkish color and a low alkaline pH which becomes acidic over time, reaching 3.8. Once harvested, it does not form clots and does not give off an unpleasant smell of decomposing proteins. It remains fluid even after one year of harvesting and has very high chemical stability. On the other hand, the mechanical stability of mangabeira latex is very low, coagulating with the action of strong agitation (PINHEIRO *et al.,* 2004). These information are important for the development of new therapeutic products.

Considered a biomaterial, it has been used for the production of biomembranes, and its physical, chemical and mechanical characterization has shown a main component, cis-1,4-polyisoprene, also found in the natural latex of *Hevea brasiliensis* (PEGORIN *et al.,* 2021). Previous phytochemical studies have reported the identification of different classes of compounds in HS stem latex extracts, namely chlorogenic acid, naringerin-7-O-glycoside, catechin and proanthocyanidins. Naringerin was reported to be one of the main compounds of the latex (DOS SANTOS NEVES *et al.*, 2016).

Latex toxicity was also evaluated in mice. Oral administration of latex at a dose of 100 mg/kg did not induce any toxic effects, no behavioral changes, gastric injury or bleeding. After this period, the animals were sacrificed and their stomachs removed. The number of gastric lesions (single or multiple erosion, ulcer or perforation) as well as local hyperemia was evaluated. At the highest dose, lethality was not observed, indicating that the latex was non-toxic in mice, and it was not possible to determine the LD 50 (MARINHO *et al.,* 2011).

3.2 Main compounds with therapeutic potential in HS

Rutin

Rutin ($C_{27}H_{30}O_{16}$) or vitamin P is a flavonoid that exhibits a range of pharmacological activities, including antioxidant and anti-inflammatory effects. Nanoformulations enhanced the anti-inflammatory and antioxidant effects of this flavonoid and the *in vivo* assays using a model of paw edema, leukocyte migration, and plasma antioxidant capacity showed promising results (ABOUAITAH *et al.*, 2021).

Rutin has shown especially promise in the treatment of bone resorption. In addition to decreasing the expression of resorption markers, it promoted an increase in osteocytic and osteoblast proliferation markers. It may be further studied as a potential anti-osteoporotic agent. By examining the influence of rutin on vitamin D levels and alkaline phosphatase enzyme activity, it was found that it would be able to influence the increase of both while decreasing the acid phosphatase, which is a marker of osteoporosis. Thus, this flavonoid increases proliferation and ossification markers in bone cells (ABDEL-NAIM *et al.*, 2018) explaining the possible osteogenic action of HS reported by some authors due to the presence of rutin (DOS SANTOS NEVES *et al.*, 2016; D'ABADIA *et al.*, 2020).

An investigation into the effects of this flavanoid on oxidative stress, proliferation and osteogenic differentiation of human periodontal ligament stem cells (PDLSCs) was carried out. Levels of reactive oxygen species were detected, oxidative stress factors were tested and PDLSC proliferation was assessed by cell count. The osteogenic differentiation of PDLSCs was also verified by alkaline phosphatase activity test. The PI3K-AKT-mTOR pathway is an important regulatory mechanism for cell growth and metabolism and the levels of these proteins were also evaluated. Rutin inhibited the release of reactive oxygen species and increased the secretion of oxidative stress factors, including superoxide dismutase and glutathione. It also promoted the proliferation of PDLSCs, increased alkaline phosphatase activity, a marker of osteogenesis, and increased the number of mineralized nodules. The authors concluded that all these mechanisms were triggered by the PI3K/AKT signaling pathway present in the inflammatory environment (ZHAO *et al.*, 2020a) however, data are still preliminary (ZHAO *et al.*, 2020b).

Another study by the same group continued investigating the activities of rutin and found that in addition to promoting the expression of osteogenic genes and increasing AKT, it also increased the phosphorylated mTOR protein. Expression levels of GPR30, which activates PI3K, were increased by rutin, which also reduced G15, a selective antagonist of GPR30. With these studies, it can be concluded that this flavonoid has therapeutic value for periodontal bone regeneration and for tissue engineering, through the mechanism of osteogenic differentiation and proliferation of PDLSCs (ZHAO *et al*., 2020b).

Rutin was also tested in animal models of induced osteoporosis, showing therapeutic effects on bone tissue.

The improvement observed in the histomorphometric bone characteristics would be associated with

the reduction of osteoclastic activity through the inhibition of IL-1β, IL-6 and TNF-α. However, further studies are needed for clinical applicability (LEE *et al.*, 2020).

Chlorogenic Acid

Chlorogenic acid ($C_{16}H_{18}O_9$) or CGA is a phenolic acid, ester of caffeic acid and (L)-quinic acid. It is also called trans-5-O-caffeoyl-D-quinate or caffeylquinic acid or 5-CQA. |It is the precursor of dicaffeylquinic acid or cyanarin in some plant species. Like many other polyphenolic compounds, it has antioxidant activity (CLIFFORD, 1999; CLIFFORD *et al*, 2003).

CGA is a naturally occurring compound found in a wide variety of plants with many important pharmacological effects, being also an important secondary metabolite. *In vitro* and *in vivo* studies have found many pharmacological effects of chlorogenic acid, such as antioxidant, anti-inflammatory, antibacterial, antiviral, hypoglycemic, lipid-lowering, antihypertensive, antimutagenic, anticancer and immunomodulatory. However, its exact mechanism of action is still unclear. There are many issues in research and development of CGA, due to the difficulty of extraction and purification, low stability, low solubility, low oral bioavailability and allergenic effect if injectable (MIAO & XIANG, 2020).

The effect of CGA on estrogen-deficiency-induced osteoporosis was observed in ovariectomized rats treated with 45 mg/kg/day of CGA. Bone loss on femoral metaphysis was assessed by microCT. Gene expression profile was analyzed for bone marrow mesenchymal stem cells (BMSCs. The gene *microarray* profile showed 121 genes expressed in BMSCs. Many genes associated with the mitogen-activated protein kinase (MAPK) pathway were altered, suggesting that this pathway may play an important role. CGA improved bone quality by modifying bone mineral density and trabecular microarchitecture. Administration of CGA in the treated group may involve the MARK signaling pathway, regulating p38 and ERK phosphorylation. In summary, CGA can counteract osteoporosis in this animal model and the microarray results combined with bioinformatics analysis suggested that the MAPK pathway may be valuable for mechanistic research in the future (MIN *et al.,* 2018).

Naringenin

Naringenin ($C_{15}H_{12}O_5$) chemically known as 5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one is a common dietary polyphenolic constituent of citric fruits. It has received considerable attention for pharmaceutical and nutritional development due to potent pharmacological activities and therapeutic potential. Growing evidence from *in vitro* and *in vivo* studies has revealed multiple biological targets along with complex underlying mechanisms, suggesting possible therapeutic applications of naringenin in various neurological, cardiovascular, gastrointestinal, rheumatologic, metabolic, and malignant disorders. Functionally, this enhancing effect of naringenin is mainly attributed to its anti-inflammatory effects (via inhibition of cytokine recruitment and inflammatory transcription factors and antioxidant effects (via free radical scavenging, reinforcement of the endogenous antioxidant defense system and chelation of metal ions). This biocompound may be a potential agent as a dietary adjunct in the treatment of many human diseases (RANI *et al.*, 2016). These reports may perhaps explain the positive action of the consumption of products derived from HS, since naringerin was reported to be one of the main compounds of the latex

(DOS SANTOS NEVES *et al.*, 2016).

Presented data indicated that naringerin would be a safe anti-SARS-CoV-2 agent, endowed with inhibitory activity of this coronavirus. These findings offer a potential molecular model for infection by this virus, with naringerin being a candidate drug target for future experimental *in vivo* trials aimed at improving the management of patients with COVID-19 (CLEMENTI *et al.*, 2021).

From a pharmacogenetic perspective, the effect of TPCN2 genomic variants may be of primary interest if naringerin is tested as an experimental drug against SARS-CoV-2 in humans. TPCN2 gene variants may be associated with drug response and should be considered as a relevant variable in clinical studies (DI MARIA, MARTINI, GENNARELLI, 2021).

L-(+)-Bornesitol

Bornesitol, $C_7H_{14}O_6$, is a *myo*-inositol methyl derivative found in several plant species (ENDRINGER *et al.*, 2007; GOMES *et al.*, 2018; MOREIRA *et al.*, 2019; 2020).

It belongs to the class of natural products named carbasugars or cyclitols. *Myo*-Inositol is an isomer of glucose acting as a precursor in the phosphatidylinositol cycle and has been marked as nutraceutical product (ENDRINGER *et al.*, 2007).

Bornesitol has been widely investigated as a compound of HS (PEREIRA *et al.*, 2015; GOMES *et al.*, 2018; MOREIRA *et al*., 2019; 2020; DE OLIVEIRA YAMASHITA *et al.*, 2020), mainly in relation to its therapeutic property in cardiovascular diseases such as hypertension (SILVA *et al.*, 2016; GOMES *et al.*, 2018; MOREIRA *et al.,* 2019; 2020).

A study on the therapeutic action of this compound, identified in HS, concluded that further investigations should be carried out for the future development of new drugs, including for the prevention of cancer (ENDRINGER, BRAGA, PEZZUTO, 2009).

3.3 Possible therapeutic activities of HS

Anti-inflammatory action

Some studies have evaluated the anti-inflammatory potential of HS (MARINHO *et al.*, 2011; REIS *et al.,* 2019; BITENCOURT *et al,* 2019; DE OLIVEIRA YAMASHITA *et al.,* 2020; VAUCEL *et al.*, 2021). The effect of HS was compared with acetylsalicylic acid in an inflammation model induced by formalin in mouse paws. Edema, cell migration, exudate volume, protein extravasation, nitric oxide, prostaglandin E2, TNF-α, IL-6, expression of inducible nitric oxide synthase enzymes and cyclooxygenase 2 were evaluated. HS latex (0.1-1.3 mg/kg) reduced edema, cell migration, exudate volume, protein extravasation, levels of inflammatory mediators (nitric oxide, prostaglandin E2, TNF-α and IL-6) and the expression of the enzymes nitric oxide synthase and cyclooxygenase 2, confirming the significant anti-inflammatory activity as well as analgesia (MARINHO *et al.,* 2011).

It is interesting to consider that studies have already reported that excess production of nitric oxide and inflammatory markers can worsen the prognosis of patients with COVID-19 and the control of nitric oxide precursors, reducing its production, could be considered in the treatment of patients affected by SARS-Cov-2 (GRIMES *et al*., 2021; PEDRAZINI, DA SILVA, GROPPO, 2022).

The potential anti-inflammatory effect of HS may be associated with the presence of naringerin, which was once considered a potent anti-inflammatory agent (RANI *et al*., 2016). In addition to its anti-inflammatory capacity, studies are being carried out inferring that this compound also has an anti-SARS-CoV-2 action by inhibiting the activity of the coronavirus (CLEMENTI *et al*., 2021), which makes HS a potent source of research.

Another worrying factor that results in a high inflammatory response is the encounter between humans and scorpions. Its stings lead to numerous medical consultations and hospitalizations, sometimes in intensive care (VAUCEL *et al.*, 2021).

The Scorpion sting causes a large inflammatory effect, characterized by local (pain, edema and redness) and systemic effects (vomiting, diarrhea, tachypnea, bradycardia and tachycardia). In more severe cases, the patient can develop cardiogenic shock and acute pulmonary edema, leading to death. The pathophysiological mechanism involved in the development of acute pulmonary edema has not yet been fully elucidated and may be related to cardiogenic or non-cardiogenic mechanisms associated with an inflammatory response. The conventional treatment for severe and moderate cases is antiscorpionic or antiarachnidic serum. Serum therapy is the most effective treatment, but it has limitations, since it is not capable of regressing the intense inflammatory response developed by the presence of toxins, as well as the little ability to reverse the cardiovascular changes generated by the massive release of catecholamines (PUCCA *et al.*, 2015). In this scenario, medicinal plants have shown benefits for the treatment of scorpion stings, and can be used as a therapeutic alternative in cases of envenoming (SOUZA LIMA *et al.*, 2017) and the mangaba juice was test in this situation.

Mangaba juice (800 g of fresh fruit with purified water) was obtained by turbo-extraction for 5 min, frozen/ lyophilized, and dissolved in water for biological assays. Rats of both sexes were poisoned with scorpion venom doses sufficient to create pulmonary edema without killing the animals, and then randomly selected to receive treatment with either phosphate saline solution or HS juice. Another division was defined as the treatment performed one hour before envenomation or immediately after. After two hours the animals were killed, and the lungs were examined. HS fruit juice inhibited the inflammatory effects of acute lung edema and poisoning-induced kidney damage. The anti-inflammatory potential can be attributed, at least in part, to the presence of phenolic derivatives identified in the fruit juice (chlorogenic acid and rutin), which can act in synergy for the development of this activity (DE OLIVEIRA YAMASHITA *et al.,* 2020).

In another study, mice were injected with the venom of *T. serrulatus* (TsV, 0.8 mg/kg) intraperitoneally, and treated intravenously with the aqueous extract of HS (20, 30 and 40 mg/kg), the arachnid antivenom (50 μL), dichloromethane, ethyl acetate and n-butanol fractions of HS (20 mg/kg), as well as rutin and chlorogenic acid (2, 2.5 and 5 mg/kg). Leukocyte migration to the peritoneal cavity was reduced as well as the levels of IL-1β, IL-6 and IL-12 with the therapeutic use of aqueous extract, fractions, and phenolic compounds. In addition, pulmonary histopathological analysis showed a reduction in interstitial and alveolar edema, as well as in leukocyte infiltration and vascular ectasia in the lung of mice, which shows a protective effect attributed to HS. It has been suggested that the bioactive compounds in the aqueous extract, mainly chlorogenic acid and rutin, are responsible for the plant's anti-inflammatory activity (BITENCOURT *et al.*, 2019).

Another pathology that comes from an inflammatory process is gastrointestinal disorders such as constipation and some natural products have properties that contribute to the reduction of the inflammatory

process. HS pulp was also evaluated as an inducer of intestinal motility through supplementation of different concentrations in rats. Forty male rats were divided into five groups and evaluated for 14 days. Food intake, weight gain, ionic balance, intestinal motility and histopathological analysis of the small intestine, large intestine and liver were evaluated. Supplementation with mangaba pulp at its highest concentration (15 mL/kg) caused a 15% increase in the distance covered by charcoal flour as well as a decrease in serum levels of magnesium and white blood cells in the small and large intestine. The results suggest that mangaba pulp has laxative and anti-inflammatory properties and that its consumption is beneficial and should be encouraged (REIS *et al.*, 2019).

Antimicrobial action

Several parts of HS are used in folk medicine and the leaf and/or bark extract, in addition to presenting anti-inflammatory, antihypertensive, antidiabetic properties, also has antimicrobial activity. The antimicrobial activity was determined by calculating the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), minimum fungicidal concentration (MFC) and zone of inhibition. Antimicrobial activity was observed against American Type Culture Collection (ATCC) and hospital strains of dermatophyte bacteria and filamentous fungi. The antioxidant activity was demonstrade by inhibiting hemolysis, scavenging free radicals, and inhibiting lipid peroxidation in human erythrocytes. The cytotoxic activity of EEHS was evaluated by activation of cathepsins, reduction of mitochondrial membrane, and apoptosis. The results indicated the presence of phenolic and flavonoid compounds in EEHS with antioxidant, antimicrobial, and cytotoxic activities. It was found that EEHS was effective against all microorganisms evaluated, including a gram-positive strain (*S. aureus*) and a gram-negative strain (P. mirabilis), but showed bacteriostatic and fungistatic activity against a gram-negative strain (*K. pneumoniae*) and the yeast *Candida albicans*, respectively. Furthermore, all ATCC strains were more sensitive to the action of EEHS when compared to hospital strains, except for *K. pneumoniae* and *C. albicans*, which showed the same MIC (SANTOS *et al.*, 2016).

Another study compared the antimicrobial activity of extracts from HS leaves, HS bark and the leaves of *P. grandis* (boldo-grande) against *Escherichia coli*, *Staphylococcus aureus* and *Klebissiella pneumonae*, as well as a *Candida albicans* strain. An halo in the culture medium denoted the inhibition of *Staphylococcus aureus* (gram-positive), *Escherichia coli* (gram-negative) and *Candida albicans*. There was no formation of halos on medium with *Klebsiella pneumoniae* (gram-negative). All positive controls confirmed their degree of inhibition according to the established parameters and corresponding to the behavior of the strains used. It was concluded that the extracts of both HS and *P. grandis* have antimicrobial action against some bacteria used, evidencing their use in folk medicine against some infections affected by *Staphylococcus aureus* and *E. coli* (CORDEIRO *et al.*, 2019).

The antifungal activity of HS latex was also observed against *Candida albicans*. Latex bacterial communities from three HS trees were characterized using traditional molecular plating methods. Twelve strains isolated from latex samples were separated into four groups by restriction analysis of amplified ribosomal DNA. A representative of each group was sequenced, and they were identified as belonging to the genera Bacillus, Klebsiella, Enterobacter and Escherichia. None showed antifungal activity against *C. albicans*, concluding that this latex activity has no microbial origin. It was also concluded that the presence

of some potential pathogens should be considered before the use of H. speciosa latex in folk medicine (SILVA *et al.,* 2011).

Antihypertensive action

Systemic arterial hypertension (SAH) is characterized by constant blood pressure values ≥ 140x90 mmHg and is caused by a multifactorial condition such as genetic/epigenetic factors, age, diet, and physical inactivity. Its treatment ranges from lifestyle changes to drug monotherapy or therapies combined with more than one drug, and the control of hypertension is essential to avoid hypertensive crises with a high potential for vascular accidents (PEDRAZINI & GROPPO, 2020; PEDRAZINI *et al.*, 2022).

The antihypertensive activity of HS has already been demonstrated and attributed to the presence of polyphenols and cyclitols such as l-(+)–bornesitol, a bioactive marker. Bornesitol used in one study was isolated from HS leaves and subjected to forced degradation conditions, being classified as unstable for acid and alkaline hydrolysis but very stable for exposure to oxidative and neutral hydrolysis and for degradation by photolysis. It presents a large reduction in its content when exposed to metal ions or thermolysis. Bornesitol samples were degraded by neutral hydrolysis, thermolysis and tested *in vitro* for inhibition of ACE (angiotensin converting enzyme) showing a substantial decrease in biological ACE activity (GOMES *et al.*, 2018).

Another study aimed to investigate the ability of bornesitol, one of constituent of the leaves of this plant, to reduce blood pressure and its mechanism of action. Normotensive Wistar rats were divided into a control group and a group treated intravenously with bornesitol (0.1; 1.0 and 3.0 mg/kg) and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded in awake, non-anesthetized animals. Nitric oxide (NO) and angiotensin-converting enzyme (ACE) were measured in plasma using colorimetric methods, the study of vascular reactivity was performed in rat aorta rings and the involvement of nitric oxide synthase (NOS) was investigated in the vasodilator effect. Bornesitol administration significantly reduced SBP, increased nitrite plasmatic level and decreased ACE activity in normotensive rats, and in rat aorta, bornesitol induced endothelium-dependent vasodilation, which was abolished by NOS blockade. Bornesitol reduced blood pressure by a mechanism involving increased production or bioavailability of NO and inhibition of ACE. The results supported the use of bornesitol as an active marker of cardiovascular activity in HS (MOREIRA *et al.*, 2019).

Other researchers have also focused on the inhibitory potential of bornesitol on ACE, investigating the pharmacokinetic properties of this compound administered orally to Wistar rats, as well as its permeation in Caco-2 cells, quantifying its plasma concentration in rats. Pharmacokinetics were evaluated by administering single doses intravenously in bolus (3 mg/kg) and gavage (3, 15 and 25 mg/kg) and permeation, tested in a Caco-2 transwell cell model, was tested with bornesitol alone, or combined with rutin, or as a constituent of HS extract. Bornesitol showed low permeability in Caco-2 cells, but permeability apparently increased when administered in combination with rutin or as a constituent of HS extract. The data obtained may be useful to guide the development of herbal preparation from HS containing bornesitol as an antihypertensive agent (MOREIRA *et al.*, 2020).

The ethanolic extract of the leaves of HS promotes vasorelaxant effects in the aorta and mesenteric arteries of rats through the production of nitric oxide (NO) by endothelial cells via activation of phosphatidyl

inositol 3-kinase (PI3K). Based on this assumption, hypertension was induced in mice. HS leaf extract at concentrations of 0.03, 0.1 or 1 mg/kg by gavage induced a dose-dependent and long-lasting reduction in systolic blood pressure in animals with hypertension. The administration of the extract produced a significant increase in the plasma level of nitrites. The extract also induced a concentration-dependent vasodilation of mesenteric arteries contracted with phenylephrine. These results pointed to an antihypertensive effect of the extract of HS leaves due to the reduction of peripheral resistance by the production of NO and by a mechanism that involves the increase of the production of H_2O_2 in the mesenteric arteries of hypertensive mice. These findings may support the use of *Hancornia speciosa* by traditional medicine as an antihypertensive drug (SILVA *et al.*, 2016).

Antihyperglycemic action

Diabetes has become a common lifestyle disorder associated with obesity and cardiovascular disease. As current antidiabetic drugs have unprecedented side effects, traditional herbal medicine can be used as an alternative therapy. An *in silico* analytical tool helps to unravel the multi-targeted action of herbal formulations rich in secondary metabolites and bring together the databases on medicinal plants for diabetes and associated diseases, their bioactive compounds, possible diabetic targets, drug-receptor interaction, and toxicology reports that can open a corridor into safer, more effective, and toxicity-free drugs (VENKATESWARAN *et al.*, 2021).

A hypothesis exists about the benefits of HS on high glycemic levels, which could help prevent complications in diabetes. The lack of a scientific report that proves the great use of this plant for the treatment of diabetes, led a group of researchers to investigate whether HS would exert beneficial effects on hyperglycemia, preventing diabetic complications using the aqueous extract of mangabeira leaves on parameters metabolism of diabetic rats (NETO *et al.*, 2020).

The study was based on information that in non-diabetic mice, a single dose of HS leaves (300 mg/kg of ethanolic extract) inhibited intestinal α-glucosidase *activity in vitro* and stimulated glucose uptake in adipocytes, decreasing the blood glucose level. The ethanolic extract of HS leaves and its fractions were evaluated for inhibition of the hyperglycemic effects of starch or glucose. The result showed inhibition of α-glucosidase *in vitro* but only the crude extract and the dichloromethane fraction inhibited the hyperglycemic effect induced by starch or glucose, in addition, they were also able to increase glucose uptake by adipocytes. Bornesitol, quinic acid and chlorogenic acid were identified in the extract, together with the flavonoid glycosides, while the dichloromethane fraction is mainly composed of lupeol esters and/or α/β-amyrin. HS, in this study, was shown to have a potential effect on hyperglycemia through a mechanism dependent on α-glucosidase inhibition and increased glucose uptake (PEREIRA *et al.*, 2015).

HS also seems to have a beneficial action in preventing complications in diabetics. To evaluate this potential, diabetic Wistar rats were treated with an aqueous extract from the leaves of the plant (400 mg/kg) and the metabolic parameters of the diabetic animals were analyzed. The oral glucose tolerance test was performed and the area under the curve (AUC) was estimated at the 17th day. The study period was 21 days and the analyzes were performed both on blood samples and in the animals' organs. Treatment with HS in the non-diabetic control group did not change the initial parameters. In severely diabetic animals, which initially had decompensated hyperglycemia, polydipsia, hyperphagia and dyslipidemia, the treatment with

HS caused lower blood glucose, AUC, dyslipidemia parameters and relative organ weights compared to untreated diabetic rats. These results signaled that the HS leaves extract could be a safe alternative to control some complications associated with type 2 diabetes (NETO *et al.*, 2020).

Gastroprotective action

HS is frequently cited in ethnopharmacological inventories against gastrointestinal disorders such as diarrhea, ulcers, gastritis, and stomach pain (ALMEIDA *et al.,* 2019a). The hydroalcoholic extract and HS bark infusion were investigated for their ability to prevent and cure gastric ulcer in rodents. Its preventive and healing action was evaluated in experimental models in rodents with gastric pathologies like those in humans. The bark infusion had no gastroprotective effect, however, the hydroalcoholic extract (500 mg/kg) decreased the severity of gastric damage induced by HCl/ethanol, indomethacin/bethanechol, stress or pylorus ligation, due to increased local pH, decreased gastric acid production, and increased amount of mucus (3.62 mg/tissue weight and 5.81 mg/tissue weight respectively). Another observation was that the hydroalcoholic extract had healing action and anti-Helicobacter pylori effect. It was concluded that HS would have an anti-ulcer action due to its potential to increase the formation of gastric mucus, the ability to reduce the secretion of stomach acids and its antioxidant properties thanks to the polymeric proanthocyanidins present in the composition of the bark without having toxicological effects at the dosages used (MORAES *et al.* 2008).

Hepatoprotective action

More than 1 million people die every year from liver failure and one of the causes is the indiscriminate use of paracetamol (acetaminophen). Liver cytochrome P-450 enzymes uncontrollably produce N-acetyl-p-benzoquinone imine (NAPQI) when high doses of acetaminophen are ingested. Ingestion of more than 350 mg/kg of this drug, an analgesic and antipyretic, leads to liver damage (ASRANI *et al.*, 2019).

Mangaba juice, widely used in folk medicine as an anti-inflammatory, also suggests antioxidant and hepatoprotective activities. Wistar rats in paracetamol-induced hypotoxicity models (900 mg/kg) were previously given preventive treatments for 10 days and in two groups there was fruit extract (200 mg/kg). The evaluation of the hepatoprotective effect included liver function tests showing a reduction of markers in the animals that received the fruit extract, AST (reduced by 37.90%), ALT (38.42%) and GGT (59.73%) analyzed in the serum ($p<0.05$). Histopathological analysis of the liver revealed that HS reduces hepatocellular degeneration and chemical characterization revealed 16 different phenolics, with chlorogenic acid (150±5 µg/g) and rutin (120±8 µg/g) being the main ones. These data confirmed that these phenolics can prevent acetaminophen-induced liver injury. The hepatoprotective effect occurs through the inhibition of lipid peroxidation promoted by chlorogenic acid and rutin. Its is known that further studies are needed to elucidate the detailed mechanism of this hepatoprotective effect (CHAVES *et al.*, 2020; SANTOS *et al.*, 2022).

Another phytochemical study analyzing the lyophilized extract of HS, found the presence, in a relevant concentration of zinc and boron. Zinc is an important factor for antioxidant enzymes and boron supplementation and has been shown to improve liver antioxidant activity in animals (BHASKER *et al.*,

2017) suggesting increasing the hepatoprotective activity of HS and maintaining high antioxidant enzyme activity (SANTOS *et al.*, 2022).

Dermo protective action – wounds

About 1% of the western population suffers from venous leg ulcers that require intensive treatment and long-term care. The main risk factors are old age, obesity, diabetes, lack of nutrients, chronic disease, previous leg injuries, deep vein thrombosis and phlebitis. The use of biomaterials has shown promise in the quality of life of these patients and among the available biomaterials are biocompatible natural polymers, such as natural rubber latex, cellulose, chitosan, and alginate (PEGORIN *et al.,* 2021).

The bioactives present in natural vegetable latex when in small amounts are difficult to isolate and have low bioavailability and stability. Nanotechnology has presented advances offering nanomaterials as nanocarriers of natural pharmacologically active latex agents. The conjugation of natural latex nanocompounds with nanoparticles, liposomes, micelles, nanodiamonds and carbon nanotubes allows to improve the bioavailability and stability of natural compounds derived from pharmacologically active latex. Nanoscience has focused on the potential for controlled drug delivery at specific sites using the therapeutic potential of latex (WAROWICKA, NAWROT, GOŹDZICKA-JÓZEFIAK*,* 2020).

HS latex incorporated with nanoparticles, has been widely studied showing high efficiency in the anti-biofilm activity *in vitro* and does not harm the subcutaneous tissue in *in vivo* analysis, suggesting it could be a promising material for future applications in the area of skin wound regeneration (BONETE *et al.*, 2020).

Membranes made with *Hevea brasiliencis* latex were developed to serve as a dressing in exuding wounds of diabetic patients. Initial results showed that the presence of latex favored the proliferation of fibroblasts (BARROS *et al.,* 2021), but like the latex from *Hevea brasiliensis,* the latex from HS has been studied for new medical applications and among them are the treatment of skin wounds. The values of the elasticity modulus were close to those of human skin, in addition, cell biocompatibility and non-toxic characteristic were found, concluding that it is a safe and biocompatible biomaterial for the wound healing process due to its ability to stimulate inflammatory cells and initial angiogenesis. In addition, the study in an animal model showed an increase in collagenesis and an improvement in the quality of the healing process, suggesting that it is a good alternative to existing materials with the same function (PEGORIN *et al.,* 2021).

Several plants have potential for the new drugs development and among the laticiferous plants, the best known and most exploited latex for this purpose is the rubber tree *Hevea brasilienses* (a Brazilian native tree known as “Seringueira”), which has an angiogenic property. One fraction of rubber tree latex gave rise to Regederm®, a cream-gel used in the treatment of tissue injuries (Pelenova Biotechnology SA, http://www.pelenova.com.br). However, there are reports of an allergenic potential of this latex, so the search for other latex producing species with lower allergenic potential has been the researcher’s goal. HS appears to be one of these laticiferous plants whose latex has a lower number of biocompatible proteins with angiogenic properties and lower allergenic potential. The serum fraction was responsible for the highest angiogenic activity, revealing an expressive presence of flavonoids and tannins, compounds with great pharmacological importance because they are substances that have antimicrobial and antioxidant potential. These characteristics, associated with the angiogenic potential, can act in the acceleration of

tissue regeneration.The main compound identified was chlorogenic acid (CGA), an ester of caffeic acid and quinic acid, with CGA being the main secondary metabolite of the latex serum fraction. An *in-silico* analysis predicted metalloproteinases as targets of the CGA which seems to interact with the cavity of the active site of this metalloproteinase. It has been suggested that CGA can regulate extracellular matrix remodeling and stimulate the healing process, but it must be confirmed in animal studies and/or in clinical trials (D'ABADIA *et al.*, 2020).

Silver nanoparticles (AgNP) were also added to HS latex to compose a functional biomaterial associating the intrinsic angiogenic activity of latex and the antimicrobial activity of silver. Membranes without silver and with silver (0.05% and 0.4%) were implanted on the back of female rats observed for 3, 7 and 25 days. It was observed that the incorporated nanoparticles did not change the anti-inflammatory and angiogenic activity of the latex, but in relation to the formation of bacterial biofilm by Staphylococcus aureus and the antimicrobial activity, the membranes composed of HS and AgNP at 0.05% and 0.4% showed an induction to cremation, *i.e*., a plasmolysis of the bacteria as well as a protective action against the apposition of biofilm on the membrane. These results showed a positive behavior of the biomaterial for its use in tissue repair due to the power of angiogenesis, which is the first desired step in the healing process and inherent to HS as the bacterial control inherent to AgNP. These observations are of great importance for the development of healing materials (BONETE *et al.*, 2020).

Latex from different species is capable of producing tissue replacement and regeneration, but the biomembrane obtained from HS latex have once again shown high angiogenic as well as osteogenic activity. With an interest in wound healing, researchers wanted a combination of antibacterial and antifungal activity also using silver nanoparticles (AgNP). To combine angiogenic, antibacterial and antifungal properties on the same platform, they developed an HS membrane containing 3 concentrations of AgNP (0.1%, 0.2% and 0.4%). This biomembrane successfully accommodated AgNP in the matrix, released it in a controlled manner (drug delivery) and the dynamics of AgNP release by the biomaterial was observed by UV-vis absorption spectroscopy. At the concentrations studied, there were no cytotoxic effects on the union of HS with AgNP. The genotoxic effect was observed at the two highest concentrations but absent at the lowest concentration. It was noticed that the addition of AgNP (0.1%) can improve the pharmacological activity of the HS membrane without causing a toxic effect on plant cells. This new biomembrane combines angiogenic, anti-inflammatory and antibacterial activities and although results obtained with the plant model show a high degree of compliance with results obtained in tests with mammals. New preclinical studies should be performed in animals to establish the appropriate dose so that it can be considered a potentially new biomaterial for wound healing (ALMEIDA *et al.*, 2019b).

Osteogenic action

To assess the osteogenic potential of the latex, it was diluted at 3% and 50% with distilled water and administered by gavage daily (0.5 mL) in a total of 28 Wistar rats that underwent surgery to create a defect of 5 mm in diameter, in the parietal bone. This experiment was carried out in 2 different periods, 15 and 30 days, and in each period, there were 3 groups: control group with distilled water, 3% latex group and 50% latex group. The calvaria was collected and the results showed that the experimental groups had the same amount of neoformed bone in the calvaria defect as the control group, concluding that oral HS,

in this study, did not contribute to the increase around neoformed bone in the calvaria defect, however, the data obtained may be related to the way of administration. It is known that latex obtained from the trunk of *Hevea brasiliensis* can be an innovative biomaterial for bone repair and some experiments that were carried out with this product showed improvement in bone repair of dental cavities in rats, in guided regeneration in rabbit calvaria and in bone repair of a critical defect in rat calvaria, but the osteogenic potential of HS still requires further research. Some communities located in the Northeast of Brazil produced a milky juice called "mangaba milk" from the latex of the trunk of HS and ethnobotanical surveys confirmed the use of this milky juice for the therapeutic treatment of bone fractures, however, no randomized clinical study was performed to confirm this effect (FELIPETTI *et al*., 2019).

However, a new study was carried out with a similar methodology, confirming that the oral use of latex would not increase neoformation, but the mineralization of the neoformed bone due to the presence of calcium in the HS latex, concluding that there is a potential in the development of new drugs for bone mineralization (FELIPETTI et al, 2022).

An *in vivo* study also evaluated the osteogenic potential of HS latex and the cytotoxicity of its aqueous phase. The phytochemical profile and osteogenic potential of a gel containing 5% of *Hancornia speciosa* latex were observed after application to a critical calvaria defect in rats, as well as to intact calvaria. After 3 days of application of the gel on the periosteum of the intact calvaria, it was enlarged and thicker than the control. Neoformed bone was observed after 5 and 11 days, and there was also an increase in the proliferation of periosteal cells. The area of newly formed bone at the edges of the calvaria defect was greater in rats that received the gel 15 and 30 days after surgery. Furthermore, the cytotoxicity of the aqueous phase of latex was evaluated in rat calvaria cells *in vitro,* demonstrating a reduction in cell viability at concentrations above 0.6 mg/mL. Chlorogenic acid, naringenin-7-O-glucoside, catechin and procyanidin were identified in the aqueous phase of latex, the first two being identified as the main agents with the greatest osteoinductive potential (DOS SANTOS NEVES *et al.*, 2016).

In addition to these compounds, the presence of rutin has already been described in the literature, both in the pulp extract and in the leaves (DE OLIVEIRA YAMASHITA *et al.,* 2020; SANTOS *et al.,* 2021; CAMPOS *et al.*, 2021), and this flavonoid increases proliferation and ossification markers in bone cells (ABDEL-NAIM *et al.*, 2018; ZHAO *et al*., 2020b). Rutin may also exist in latex which also would explain, in the study by dos Santos Neves and col. (2016), the possible osteogenic activity inferred by the author.

4 CONCLUSIONS

There is already evidence on the importance of dietary balance, considering the compounds contained in the food such as amino acids, in controlling the evolution of some diseases (PEDRAZINI, DA SILVA, GROPPO, 2022). In addition, molecular data, such as genetic sequences and amino acids present in plants such as HS, are extremely important to identify a species, as well as to assess its potential as a food (NUNES *et al.*, 2022) and as a basis for the development of new drugs with fewer side effects (PEDRAZINI, DA SILVA, GROPPO, 2022; NUNES *et al.*, 2022).

It is known that the main challenge in the herbal medicines use is the lack of a fully elucidated mechanism of many compounds action, which can affect human health in long-term consumption, since plants have metabolites that can be dangerous. Even though traditional herbal medicines have beneficial

effects with antioxidant, antihypertensive, hypoglycemic, lipid-lowering properties, among others, proving to be safe and with fewer side effects when compared to synthetic drugs, it is important to try to gather data on medicinal plants, detailing their origin, absorption mechanism, distribution, metabolism, excretion, toxicity, their bioactive compounds, possible therapeutic targets and drug-receptor interaction. In this way, a path is opened with safer, more effective drugs with known or even non-existent adverse effects (BAILÃO *et al.*, 2015; VENKATESWARAN *et al*., 2021).

Medicinal plants are widely studied regarding the anti-inflammatory and antioxidant properties of bioactive agents, however, the challenge for clinical applicability is related to low bioavailability, low water solubility and difficult-to-control release kinetics. Nanotechnology can offer innovative solutions that can enhance the therapeutic activity and control the release kinetics of these agents, providing greater safety in clinical use (ABOUAITAH *et al.*, 2021).

It is important to consider the great challenge in the study of plants as an alternative therapy. The same plant can have an anti-inflammatory power by reducing the production of nitric oxide (MARINHO *et al.,* 2011) and at the same time be antihypertensive by increasing the production of nitric oxide (MOREIRA *et al.*, 2019). These questions only show the need to identify components and the usefulness of each one and confirm that the misuse of phytotherapy can bring more harm than benefit.

Brazil has several biomes with high biological diversity and native species, often used as medicinal plants. The study of the pharmacological properties of these plants used in conventional medicine guarantees their scientific record and strengthens the traditional knowledge accumulated over the centuries. *Hancornia speciosa* Gomes has been described as a highly versatile species, being traditionally used in the treatment of several diseases, having a high economic and biotechnological potential for the development of new medicines using its leaves, latex, fruits, and bark (DOS SANTOS *et al.*, 2018). (Fig.2 A,B,C,D)

A greater knowledge of the population and health professionals about scientific research related to the therapeutic use of plants, therapeutic doses, contraindications, side effects and risks of drug interactions between the different species of popular use, as well as with allopathic formulations, will minimize accidents (FREIRE *et al.*, 2021).

Faced with so many studies and results presented, it can be concluded that the use of medicinal plants should be valued as well as popular knowledge about its applicability however, it is necessary to warn about the possible side effects of indiscriminate use and about the possible interactions between the chemical compounds, the botanical, ethnobotanical and pharmacological aspects of plants with other drugs and even with those of another plant. Due to the rich content of bioactive compounds, *Hancornia speciosa* Gomes may be a promising choice for nutraceuticals and therapeutics, but from a scientific point of view, more *in vivo* studies are needed to standardize dosages, evaluate pharmacodynamics, pharmacokinetics and toxicology, especially in relation to the use of latex with the potential presence of pathogens in its composition during its extraction. Randomized clinical studies based on the knowledge and popular use of this plant should be carried out after other pre-clinical studies to prove its efficacy and safety.

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Gomes' photos from a plantation in the Cerrado biome – Bahia State.

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