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EVIDENCE OF THE USE OF MEDICINAL PLANTS IN THE TREATMENT OF SYSTEMIC ARTERIAL HYPERTENSION

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ABSTRACT

Introduction: Systemic Arterial Hypertension is one of the biggest health problems worldwide and a crucial factor in the worsening of cardiovascular diseases in the population, so its existence encourages the development of a range of treatments both for controlling symptoms and improving the patient's quality of life. Thus, phytotherapy enters as one of the other types of therapeutic approach, since many phytotherapeutics have unique molecules in their composition, some of which have the potential to benefit health, such as flavonoids and polyphenols, so this article seeks to recognize plants that have useful properties in combating hypertension that are common in Brazil. Methodology: In this context, through a retrospective, cross-sectional study using the PubMed, webofscience, Lilacs, Pubmed, and Google Scholar platforms, based on the keywords antihypertensive, arterial hypertension, high blood pressure, phytochemical, and phytotherapy. Results and Discussion: Seven plants were found whose antihypertensive properties were reported with evidence through clinical trials in animals or people, namely Cymbopogon citratus (Lemongrass); Bidens pilosa (Black thistle); Allium sativum (Garlic); Oryza sativa (Rice); Hibiscus sabdariffa (Sour okra); Cuphea ignea (Saint Anthony's flower); Ocimum basilicum (Basil) and Melicoccus bijugatus (Mamoncillo). Conclusions: Some mechanisms of action of these herbal medicines can be suggested through the studies carried out, however, to categorically understand the efficacy and pharmacology of any of these active ingredients, a more in-depth specific study is necessary.

Keywords: Antihypertensive. Arterial Hypertension. Medicinal Plants. Phytotherapy.

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INTRODUCTION

The World Health Organization (WHO) considers Systemic Arterial Hypertension (SAH) to be a chronic disease characterized by systolic pressure above 140 mmHg and diastolic pressure of 90 mmHg, being an aggravating factor for a series of serious cardiovascular diseases, responsible for almost 18 million deaths worldwide per year (BHANDARI, 2024). Hypertension is multifaceted in its aggravations, depending on the progression of the disease, so there may be symptoms in cases where the systolic pressure is above 180 mmHg, ranging from headaches, dizziness, and even more dangerous conditions, such as cardiac arrhythmias (DAVID, 2021).

According to data from the report presented by the World Health Organization (WHO), approximately one in three adults in the world has high blood pressure. It is observed that between 1990 and 2019, the number of people with hypertension doubled, from 650 million to 1.3 billion, and still, about half of the people with hypertension do not know they have the disease and do not receive adequate treatment (WHO, 2019).

Hypertension can cause strokes, heart attacks, heart failure, kidney damage, and other health problems. In Brazil, it is estimated that 45% of adults between 30 and 79 years old have hypertension, which is equivalent to 50.7 million people. Of this total, 62% have the diagnosis, but only 33% have their blood pressure under control (SILVEIRA, 2023).

Brazil is not exempt from the global scenario, since according to the Ministry of Health, cardiovascular diseases, despite the reduction in incidence in the country, are among the leading causes of death in the Brazilian population. Diagnosed with hypertension, in 2019, approximately 5.3% of people over 18 years of age were diagnosed with some disease of this type (WHO, 2023). Thus, Brazil is in an unfavorable position, since the large number of hypertensive patients that exist and are diagnosed every year directly impacts public health. The treatment of systemic arterial hypertension has been one of the most researched, so much so that each year, new medications are introduced to the market for this control, among them, we can mention diuretics, antihypertensives, such as methyldopa, beta-blockers (metoprolol), angiotensin II converting enzyme inhibitors and, perhaps one of the most used in Brazil, angiotensin II receptor antagonists (losartan). Even with all the pharmacological advances and because systemic arterial hypertension is a practically asymptomatic disease, many patients stop using these medications, which ends up worsening over time, followed by unhealthy lifestyle habits.

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The use of medicinal plants to treat systemic arterial hypertension has been used since ancient times all over the world. In Brazil, it is no different, and it is even assumed that more plant species with medicinal properties should be used to treat hypertension, since, due to its continental dimensions and 5 defined biomes, it has the greatest biodiversity on the planet. However, there is a lack of studies that can clinically demonstrate the use of medicinal plants to treat hypertension (CAMARGO, 2023).

Extracts of bioactive compounds such as polyphenols, present in most medicinal species, emerge as an alternative to the treatment of cardiovascular conditions since many of these are frequently studied for their various properties, including antihypertensive action. (MARHUENDA et al., 2021). Despite the knowledge obtained through the isolation and identification of organic compounds, quality control of medicinal plants in Brazil is still quite precarious (CAMARGO, 2010).

Most cases of hypertension are classified as primary, that is, without an apparent cause, but a portion of the cases appear to have their pathophysiology linked to the renin-angiotensin-aldosterone system, the etiology of which is related to kidney malfunction (Maideen; Balasubramanian; Ramanathan, 2021; Mudau; Odeyemi; Dewar, 2020). Studies also report the presence of a range of alkaloids, flavonoids, and polyphenols in several plants, whose effects are hypotensive and cardioprotective, with the potential to promote a reduction in blood pressure in the short and long term (Islam et al. 2023; Reddy et al., 2022; Zeeshan et al., 2023).

Phytotherapy, through the use of medicinal plants or even herbal medicines, has emerged every day as an alternative solution to allopathic medicines, becoming popular due to its accessibility and low side effects, when compared to chemically defined drugs (Pakkir maiden; Balasubramanian; Ramanathan, 2020). Thus, this study proposes a bibliographic review to highlight the most used medicinal plants, according to popular use, in the northern region of the country, which through developed studies present clinical evidence, corroborating their use in the treatment of hypertension.

METHODOLOGY

Retrospective, cross-sectional study real, with a search using databases: PubMed, Web of Science, Lilacs, Pubmed, and Google Scholar, based on the keywords

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antihypertensive, arterial hypertension, high blood pressure, phytochemical, and phytotherapy. The search period was between 2018 and 2022, based on the title and abstract, all articles that corresponded to the use of plant species for the treatment of hypertension in the northern region of Brazil were evaluated and selected.

The articles that presented studies containing evidence for the use of medicinal plants and phytotherapeutics in the control of hypertension, which are cited, even with popular use in the northern region, were cataloged and recorded in an Excel spreadsheet. The selection criteria included studies: published in the last 5 years; adult population; evaluation of medicinal plants and phytotherapeutics with antihypertensive activities; species found in the region Brazil; Case studies, reports, conference abstracts, commentary articles, letters to the editors and policy briefs were excluded.

RESULTS AND DISCUSSION

More than 120 articles were selected, which presented citations of medicinal plants used in the control of hypertension. Of these, more than half referred to species not found in the northern region, specifically in the Amazon, and were therefore disregarded. Among the medicinal plants selected, the following plant species were listed in the articles, widely used in the Amazon region: Cymbopogon citratus (Lemongrass); Bidens pilosa (Black thistle); Allium sativum (Garlic); Oryza sativa (Rice); Hibiscus sabdariffa (Sour okra); Cuphea ignea (Santo Antônio flower); Ocimum basilicum (Basil) and Melicoccus bijugatus (Mamoncillo).

Considering the species described for controlling hypertension, information was sought regarding the tests performed on the respective medicinal plants, which in some way clinically demonstrate the hypotensive action directly or indirectly, as in the case of antioxidant metabolites. In the vast majority of articles, in vitro tests are mentioned, and some have evolved into preclinical and clinical tests.

The fact that there are not many publications of clinical tests involving medicinal plants, through their extracts, does not exclude the importance of therapeutic characterization of the respective species. Thus, new studies will be proposed to clinically demonstrate the plants mentioned in their uses for treating hypertension.

Among the selected articles, it was observed that lemongrass (Cymbopogon citratus) is an Indian herb adapted to the tropical climate that grows in bushes with long,

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thin leaves in warmer regions of several countries, such as Brazil (Figure 1) (SABOIA et al., 2022). This plant has evidence of health benefits, such as antioxidant, anti-inflammatory, and antibacterial effects (MUKARRAM et al., 2021; JOHNSON et al., 2021). In addition, the suggestion of antihypertensive action of C. citratus is also highlighted through a preclinical trial where a significant reduction in blood pressure was observed in male Wistar rats laboratory-induced to a condition of hypertension through an alcohol-saline solution.(SILVA; BÁRBARA, 2022).

Figure 1- Cymbopogon citratus (Sweetgrass)

Source: https://www.ncbi.nlm.nih.gov/datasets/taxonomy/66014/

The main biochemical mechanism by which the species, Cymbopogon citratus, has pharmacological properties that act in the reduction of hypertension, is possibly characterized by its metabolites, citral, a predominant poly aldehyde of the essential oil extracted from the plant itself, is a molecule that acts directly on cellular receptors of transient potential inducing, by some reaction chain still unknown, the vasorelaxation of the vascular endothelium (SILVA; BÁRBARA, 2022).

The species, Bidens pilosa, popularly known as Picão-preto, is a weed native to South America that, however, is present in much of the tropical regions of the world due to its great adaptability and accelerated reproduction capacity (Figure 2) (MTENGA; RIPANDA, 2022; KATO-NOGUCHI; KURNIADIE, 2024). This plant has great therapeutic potential, being used as an alternative herbal medicine for various diseases, since there is evidence of its various properties, such as anti-inflammatory, anti-allergic, and antioxidant. (RODRÍGUEZ-MESA *et al*., 2023).

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Figure 2- Bidens pilosa (Black Thistle)

Source: https://www.ncbi.nlm.nih.gov/datasets/taxonomy/42337/

Among the studies carried out with the species, mainly for the control of hypertension, there is evidence in preclinical tests in rats that Bidens pilosa can reduce blood pressure, through vasorelaxation and diuresis, although further studies are needed to determine the mechanism by which this occurs (TCHEUTCHOUA et al., 2022). Although the secondary metabolites present are known, such as simple aromatic hydrocarbons, which derive from acids such as vanillic, salicylic and protocatechuic, from phenylpropanoids and their derived phenolic acids, such as coumaric, ferulic, chlorogenic, tannic and gallic, flavonoids, which are divided into aurones, chalcones, flavanones, flavones and flavonols, terpenoids, which are divided into linear, sesquiterpenoids and triterpenoids and sterols, such as campesterol, phytosterin-B, β-sitosterol, β-sitosterol glucoside, and stigmasterol, it was not evident in the tests carried out which of the compounds would act in the control of hypertension (GILBERT, 2013). One species widely used, mainly for culinary purposes, is Allium sativum, or simply garlic. It is well-known in popular herbal medicine of Asian origin, whose bulbous flowers grow in temperate and tropical regions and are commonly used as a culinary seasoning or in homemade healing recipes (SASI et al., 2021). The pharmacotherapeutic potential of Allium sativum has been widely studied, so there is a correlation between the use of extracts of this plant and anti-inflammatory, cardioprotective, antioxidant, antidiabetic, anticancer, and antibacterial

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effects (RECINELLA et al. 2021; TUDU et al. 2022). In Brazil, it is quite common to observe the use of garlic, not only to enhance the flavor of food but also in primary health care. This use has been passed down from generation to generation and remains strong today, however, there are few or almost no studies on popular use to ensure greater safety in homemade garlic preparations. Through preclinical studies, it was also possible to observe a strong influence of Allium sativum extracts on antihypertensive activity through the direct reduction of systolic and diastolic pressure in guinea pig rats, in addition to the influence on the increase in nitric oxide levels in the body, a molecule that receptors vasorelaxation mechanisms (EL-SABER BATIHA et al., 2020).

According to El-Saber Batiha, 2020, in vivo experiments demonstrated the antihypertensive effect of the aqueous garlic extract in the 2 kidneys 1-clip hypertension model provoked in rats, reducing the level of thromboxane B2 and prostaglandin E2 and, thus, reducing hypertension in the rats tested. The dosage of garlic at a dose of 100 mg/kg for 5 days resulted in the complete prevention of acute hypoxic pulmonary vasoconstriction caused by endothelin-1, a peptide responsible for vasoconstriction in isolated pulmonary arteries of rats, and this study demonstrated that garlic reduces the production of endothelin-1 and angiotensin II (EL-SABER BATIHA et al., 2020).

Another mechanism of the antihypertensive action of the eye, with the use of extracts, was attributed to sulfur molecules present in its metabolites, which stimulate constriction and relaxation factors of the endothelium, leading to a reduction in blood pressure. It was also demonstrated in tests carried out in rats that garlic stimulates the production of nitric oxide (NO) and hydrogen sulfide (H2S), which finally leads to vasodilation (EL-SABER BATIHA et al., 2020).

Rice (Oryza sativa) is an ancient plant widely used in Brazil for its culinary properties, but outside of kitchens, it has potential in phytotherapy, since a high content of flavonoids has been detected in some species of Oryza sativa. This property can be evidenced in rice bran, which contains a range of bioactives for the health of the most diverse populations (Beaulieu et al., 2020; Suantai et al., 2022).

A study carried out on a group of 100 people, who were diagnosed with hypertension, underwent a clinical study, in which the participants ingested rice bran, and it

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was observed that the group that ingested rice bran over 12 weeks had a significant decrease in systolic blood pressure, corroborating the clinical proof of its effectiveness (OGAWA et al., 2019). Despite being a vegetable that is part of the Brazilian diet, the study debunks the belief that rice causes edema in the body and can compress blood vessels, leading to hypertension.

No other studies were found regarding the use of rice bran that could prove its use. However, the metabolites found in the species must be considered, such as starch, proteins, lipids, iron, vitamins B1, PP and folic acid, potassium, magnesium, zinc, fiber, and vitamin E, which are of great importance for the homeostatic balance of the human being. Other compounds identified in rice include vanillic, syringic, caffeic, gallic, protocatechuic, and hydroxybenzoic acids. o, sinapic and chlorogenic, and the esters 6'-O-(E)-feruloylsucrose, 6'-O-(E)-sinapoylsucrose and g-oryzanol (TIAN, 2004).

Another plant species widely used, popularly for the treatment of hypertension, is Hibiscus sabdariffa, a shrubby Indian plant with chalice-shaped leaves that has adapted to several tropical and subtropical regions around the world and which in Brazil is popularly known as Caruru-azido (Figure 3) (MONTALVO-GONZÁLEZ et al. 2022). This species is widely used in cooking, however, its therapeutic properties have been evidenced in several studies, as it presents secondary metabolites, in the polar extracts, such as flavonoids and phenolic compounds, which confer antioxidant, potentially hypoglycemic, antilipemic, and anti-inflammatory properties. (JAMROZIK; BORYMSKA; KACZMARCZYK-ŚEBROWSKA, 2022; CHO URIELLE M'BE *et al*., 2023).

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Figure 3- Hibiscus sabdariffa (Hibiscus)

Source: https://www.ncbi.nlm.nih.gov/datasets/taxonomy/183260/

Salem, et.al, 2022, carried out preclinical studies, which also suggested that hibiscus (H. sabdariffa) has antihypertensive properties. Tests on rats with hypertension, induced by L-NAME (N(G)-Nitro-L-arginine methyl ester), acting directly on the inhibition of renin during the process of increased pressure by the Renin-Angiotensin-Angiotensinogen system, results comparable to the action of captopril in the cardiovascular system (SALEM et al., 2022).

The secondary metabolites of hibiscus (Hibiscus sabdariffa) include: Alkaloids, Flavonoids, Phenols, and Tannins. Hibiscus is a plant rich in phenolic compounds, such as organic acids and flavonoids, which have antioxidant and anti-inflammatory properties (Sousa et al., 2021). One of its active ingredients is hibiscic acid, which is responsible for some of its therapeutic properties.

Another species used in the northern region as an antihypertensive, which was found in the research, was the Santo Antônio flower or cigar flower, popular name for Cuphea ignea, classified as a subshrub species of tropical and subtropical regions, whose tubular flowers give the plant its name (ISMAIL et al., 2020). In addition to its unusual aesthetics, in vivo, studies suggest a relationship between the plant's phytoconstituents and widely beneficial effects on health, with antitumor, antiviral, and antioxidant potential (Figure 4) (HASSAN *et al*., 2019; MAHMOUD *et al*., 2021)**.**

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Figure 4- Cuphea ignea (St. Anthony's Flower)

Source: Kurt Stüber - https://commons.wikimedia.org/wiki/File:Cuphea_ignea3.jpg

There is also an association via a preclinical study of Cuphea ignea, described by Hassan et.al., 2019, demonstrating hypotensive activity in hypertensive rats induced by L-NAME. The test result demonstrated that the extract of the species Cuphe ignea generated vasorelaxing action and decreased serum ACE levels by increasing the synthesis of nitric oxide in the body (HASSAN et al., 2019).

Another species used to control hypertension and which was found in the research was Ocimum basilicum, a popular spice, well known as basil, is a shrubby herb that belongs to the Lamiaceae family, found in tropical and subtropical regions of the planet (SHAHRAJABIAN; SUN; CHENG, 2020), and has several medicinal properties. According to an article published by Nabilah Sekar Azizah et al., 2023, it has potent antidiabetic, antibacterial, antiviral, and antioxidant activities.

It was also observed in another study that polar extracts of the plant also have applicability in reducing blood pressure, a fact corroborated by in vivo studies - where rats induced to hypertension by L-NAME over 1 month showed significant improvement in their systolic BP (QAMAR et al., 2023). I believe that there is a lack of information, perhaps we should discuss it further.

Melicoccus bijugatus, popularly known as Spanish lime, is a small greenish fruit with sweet and slightly citrus pulp originating from a tree that grows in tropical regions, characteristic of South America (Figure 5) (WILSON; GOLDSON-BARNABY; BAILEY, 2019). This is a plant that is not very popular but presents preclinical evidence of its effectiveness in the treatment of hypertension, and in two in vivo studies (present the studies), the plant extracts reduced the HR, SBP, and DBP of rats with hypertension induced by L-Namesic.(NWOKOCHA *et al.*, 2020).

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Figure 5- Melicoccus bijugatus (Spanish Lime)

Filo gèn' - https://commons.wikimedia.org/wiki/File:Melicoccus_bijugatus_%28Sapindaceae%29.jpg

In another experiment, Nwokocha et al., 2019, observed an effect in rats with myocardial damage caused by ischemia and reperfusion through the left coronary artery, suggesting a cardioprotective effect possibly through the reduction of peripheral vascular resistance.

CONCLUSIONS

Despite the vast medicinal flora that makes up the northern region, considering the largest equatorial forest on the planet, which includes several species with medicinal properties for various pathologies, this has aroused the interest of researchers from all over the world in studying species, mainly those native to Brazil.

Thus, it is concluded that the vast majority cited in the research are not native to the northern region, however, they are easily found and used by the local population. The popular use of these species has shown significant growth in recent years, which certainly points to technical and scientific development for more in-depth studies of these medicinal plants.

Clinical studies were conducted with some species, but in an observational manner, since there are no statistics that can measure the effects of these species on the control of hypertension in humans. Thus, it can be concluded that many studies should be carried out to demonstrate the therapeutic properties of the mentioned species to ensure access to the population in the control of systemic arterial hypertension.

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