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Research Article

Characterization of *Guazuma Ulmifolia* for the Bioprotection of Neurodegenerative Diseases: Alzheimer's Disease, Stroke and Parkinson's Disease-A Review

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Abstract

Guazuma ulmifolia is an arboreal species found in Central and South American countries, its parts are often used in the medical field, both bark, stem, leaves, and fruits. The present review study has aimed to describe the *Guazuma ulmifolia's* bioactive compounds, which have shown to be promising for the improvement of neurodegenerative diseases, such as: Alzheimer's Disease (AD), stroke (stroke) and Parkinson's Disease (PD), as based on the extant literature. In general, this plant bears antioxidant and anti-inflammatory phytochemicals, such as tannins, alkaloids, polyphenols and saponins, which suggest neuroprotection. As based on this review, we have ascertained, through its secondary antioxidant and anti-inflammatory metabolites together with other bioactive characteristics, the high potential of *Guazuma ulmifolia*, when it comes to its possible beneficial action as a neuroprotectess, however further *in vivo* researches are needed to confirm its viability as an effective herbal medicine in the treatment of neurological pathologies.

Keywords: Amazon; *Guazuma ulmifolia*; Herbal medicines; Malvaceae; Neurodegenerative diseases

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Introduction

In underdeveloped and developing countries, about 80% of the world's population consumes herbal medicines as preventive, curative treatment or even in combination with medicines [1]. Among Amazonian plants with phytotherapic potential, *Guazuma ulmifolia* has promising bioactive properties for the Alzheimer's disease, stroke and Parkinson's disease neuroprotection, as well as in the control of their secondary factors [2].

Guazuma ulmifolia is a medium spectrum tree, popularly known as guacimo or mutamba, belonging to the Malvaceae family, and can reach up to 20m high (Figure 1). It is found in deciduous and tropical forests of Central and South American countries and its growth is favorable in warm environments, around 24°C, at sea level in 1200m, in soil with good drainage and pH above 5.5 [3-5].

Figure 1: Mutamba's tree.

Brazilian *Guazuma ulmifolia* is observed in the firm ground forest of the following biomes: Amazon Forest, Atlantic Forest, Caatinga and Cerrado, which shows its great adaptation ability due to its phenotypic plasticity [6,7]. Aesthetically, its stem has long branches, is uniform, its bark is cracked, rough, brownish and internally it is pink and mucilaginous. Its leaves are greenish, simple with a serrated edge, ranging from 6cm to 12cm long and 2cm to 6cm wide; its flowers are formed by yellow petals, having a pleasant smell, which attracts bees.

The fruit is dry, egg-shaped, characterized by its yellowish and sweet pulp. It is about 2.5cm long, 1.5cm thick, while the seeds are rounded, light brown 2.0 to 2.5mm long (Figure 2) [8].

Figure 2: Mutamba's tree.

Guazuma ulmifolia is traditionally used as a treatment for several diseases, such as diabetes and hypertension. Furthermore, some of its main bioactive effects are antioxidant and anti-inflammatory activities, induced through its phytochemicals, such as: glycosides, alkaloids, tannins, glycosides, terpenoids, flavonoids and saponins [9-11]. Under this context and on account of several studies in the last twenty years on the bioactive effects of *Guazuma ulmifolia*, which have demonstrated its potential as herbal medicine and use of the local Brazilian population for this purpose.

The present article has aimed to display, through a review of the scientific literature, this tree's constituents bioactivities and, primary and secondary chemical constitution, by *in vitro* and *in vivo* researches. In addition to these issues, the *Guazuma ulmifolia* bioactive compounds effects on neurodegenerative diseases will also be specifically reviewed, with an emphasis on combating oxidative stress and neuroinflammation in the following diseases: Alzheimer's disease, stroke and Parkinson's disease, in order to ascertain their viability and potential as a herbal medicine for human use.

Chemical Composition

The *Guazuma ulmifolia* primary metabolites results vary according to the tree's part, location and age [12]. The amount of proteins in the leaf varies between 10.5% and 25%, while in the stem it comprises 38.4%-48.1%. As to carbohydrates, such as soluble sugars, nearly 13% are found in the leaf and 11.6% in the stem. In contrast, lipids and essential oil percentage shows to be in the 1% - 2.9% range [13-15]. As for the fruit, proteins represent 5.8% - 12.8%, dietary fibers 36.9% - 48.8%, sugar sucrose in the range of 16.3%, lipids 0.82% and essential oil, around 4.6%. In the case of micronutrients, the amount of ascorbic acid is approximately 13%. In what refers to minerals, nitrogen, potassium, iron and sodium, in fruits, they surpass the value of 5% [16-20]. Flavonoids, tannins, sesquiterpens, triterpenes, b-sistroloste, alkaloids, cyanogenic glycosides and diterpenes are present in *Guazuma ulmifolia* barks and leaves. The leaf holds a large amount of cardiac glycosides, phenols, terpenoids, coumarin and tannins. The fruits possess saponins, phenols, resins, quinones, triterpernoids, flavonoids, steroids, tannins and beta-carotenes. Therefore, based on the quantities of its phytochemicals, *Guazuma ulmifolia* holds pharmacological potentials such as: antioxidant, anti-degenerative and anti-inflammatory [21-23].

Anti-Inflammatory Activity

Guazuma ulmifolia puts forth a robust anti-inflammatory ability [24]. This trend occurs due to the presence of phytochemicals, such as, alkaloids, flavonoids, glycosides, saponins and phytosterols. The leaf ethanol extract showed inhibitory activity in the multiplication and change of pre-adipocyte cells, which are precursors to adipose cells, responsible for obesity, in Wistar rats. Excess and size increase of these cells lead to their inflammation in obese people, which can cause cytokines overproduction and oxidative stress in the individual's cellular metabolism [25-27].

Antioxidant Potential

Guazuma ulmifolia has a wide antioxidant activity, since its leaves ethanolic extract puts forth phenolic and flavonoids values showing 32.24±1.42µgGAE/mg and 6.48±0.14µgQE/mg, respectively. The 6.25ug⁄mL ethanolic extract was able to reduce reactive oxygen strains, in chronic kidney disease mesangial cells, *in vitro* [28,29]. Regarding the stem, the bark extract, in ethyl acetate, evinces antioxidant activity by the representative amount of total phenolics, ranging from 160.00mg/g to 373.44mg/g and flavonoids, from 23.50mg/g to 33.20mg/g [30].

The leaves flavonoid fraction methanolic extract at a concentration of 100ppm, by means of the TBA method, managed to inhibit the concentration of MDA (Malondialdehyde) by 88.52%, evincing its antioxidant activity [31]. With regards to the plant roots dichloromethane extract, there was a free radicals limiting effect through the DPPH processes, between 90% and 95% inhibition and FRAP in absorbance, between 0.4 and 1.3, both depending on the extract concentration, measured in µg/ml. In addition, its antioxidant potential has been compared to that of ascorbic acid (standard), this fact is associated with the high phenolic compounds content [32]. While the fruit ethanolic extract averaged 122.16mg/g of phenolic content and was unable to inhibit xanthine oxidase present in the process [33].

Due to possessing a significant amount of flavonoid polyphenols, tannins and alkaloids, *Guazuma ulmifolia* puts forth an antioxidant potential in the combat against neurological diseases [34]. The polyphenolic and F6 fraction of the leaf methanolic extract showed a high destruction of free radicals and the abstinence of the action of the modulated Nrf2, the modulation of this transcription factor, which has an important part in cellular homeostasis and, is the one responsible for neurodegenerative diseases.

Neurodegenerative Diseases

Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disease that leads to cognitive impairment and behavioral changes, accounting for 60% to 70% of dementia cases worldwide. It usually affects elderly people with psychological stress as a stimulator, and in those over 90 years old is named late Alzheimer's [35,36]. Alzheimer's disease bears risk factors, such as diabetes, obesity, hypertension and genetic attributes, like the presence of Apolipoprotein E (APOE) in chromosomes. Therefore, an alternative so as to prevent it, lies in changing one's lifestyle by adhering to a healthy, balanced diet and, undergoing regular physical activities [37].

Its pathophysiology can occur for three reasons: Extracellular Beta-Amyloid (BA) peptide deposition in the form of plaques in the brain; neurodegeneration, neuroinflammation, and the tau proteins intracellular grouping, known as neurofibrillar tangles [38]. The Oxidative stress is found to be one of the Alzheimer's potential aggravating factors, because when the beta-amyloid peptide joint action occurs it also does with ions in metallic form such as in iron and copper [39].

Studies show there to be no cure for Alzheimer's disease, in the USA there will be more than 13 million people affected by it in 2050, in the world around 100 million [40] and, in Brazil about 1 million, and then the trend is for it to triple [41]. As for mortality, in the USA, about 122,000 people died [42], in 2018, while in Brazil, 2,114 deaths were counted in patients admitted to hospital networks, in between 2008-2018 [43]. Therapeutic methods aim only at reducing symptoms; however, the search for medications is continuous, focusing mainly on reducing beta-amyloid accumulation and oxidative stress. In this context the search for herbal medicines is analyzed, as based on plants and their antioxidant and anti-inflammatory phytochemicals [44,45].

Regarding the bioactive activity of *Guazuma ulmifolia*, there is no research regarding neuroprotection against Alzheimer's disease. But, according to their crude, ethylic and ethyl acetate extract, the leaves showed the ability to inhibit AChE, thus promoting the action of the neutrotransmitter acetylcholine, essential for good brain function, this characteristic is related to the presence of polyphenols. Moreover, protection against beta-amyloid toxicity an important action for neuroprotection was verified [46,47].

Stroke

Stroke is a vascular syndrome that promotes a deficiency in the nervous system; it can be divided into two types: Ischemic, when there is an interruption of the cerebral blood flow; and Hemorrhagic, where there is a non-traumatic breakage of any of the cerebral blood vessels [48,49]. Some of the risk factors are diabetes, smoking, high blood pressure and stress [50]. In most cases it is brought about by atherosclerosis, inflammation and exacerbated growth of fibro muscles [51].

Stroke is the second leading cause of death in the world; in 2017 it has affected around 12 million people with approximately 5.2 million deaths, worldwide. According to WHO (World Health Organization), this disease will affect 28 million people, with 7.8 million deaths, representing approximately 12.5% of the world's mortality, in 2030. In the United States, there are about 795,000 cases per year, that may reach up to 1 million and approximately 134,000 deaths by 2050 [52-54]. In Brazil, 101,000 deaths were detected in 2017 and, there were 197,000 visits involving stroke, in SUS, in 2018. The risk groups are mainly elderly men, affecting individuals with diabetes, high blood pressure together with smokers [55,56].

Oxidative stress is an integral part of the process such as ischemic or hemorrhagic post-stroke severity, due to the fact that the excess of free radicals, through the rapid multiplication of oxygen in the recovery following the syndrome, causes cell death, bringing-about brain damage [57,58]. However, research on this subject, reports that as it is not possible to directly analyze this stress, markers like lipid peroxides, malondialdehyde, superoxide dismutase and the value of total antioxidants in plasma. Generally, these markers indicate this process to occur in the body between 3-90 days, with a higher prevalence after 24 hours of stroke; moreover, it is more recurrent in ischemic situations [59,60]. The currently used treatments do not promote a significant cure of the disease following its occurrence. But the extant therapies do consist in drugs based on antithrombotic antioxidants, that is, neuroprotectors. Under this context, herbal medicines are studied based on these properties, to have the ability to become an alternative or complementary therapy, especially considering their antioxidant capabilities [61].

There are no studies addressing *Guazuma ulmifolia* activity against this disease. However, despite there being no direct analysis on stroke, studies demonstrating its collaboration against risk factors and the main cause are available. For instance, Triandini [62], study observed that the bark effervescent powder, administered orally. At a dose of 3g/kg for fourteen days, to three-month-old mice, which had been stimulated to obesity, wound up reducing their obesity. This ability is due to the presence of some bioactive substances, such as: flavonoids, alkaloids, tannins, carotenoids, saponins and phenols. The bark acetone extract bears vasorelaxing and antihypertensive actions [63]. Furthermore, the leaves ethanolic extract was able to interrupt the HMG-CoA reductase activity by 82.6%, in the amount of 10ppm, that is, an enzyme that reduces cholesterol besides bearing a large amount of antioxidants [64], as well as the antidiabetic activity [65].

Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disease that, along with Alzheimer's, affects millions of people worldwide, specially the older ones [66]. Round about 160 in every 100,000 inhabitants, over the age of 65, in the whole world, develop this disease every year exhibiting a 1.5% mortality rate the projection of which is that the number of patients will reach up to 14.2 million cases by 2040 [67,68]. In Brazil, according to isolated studies, about 36 thousand cases per year are confirmed and, approximately 200,000 present the disease, Yet there is no official balance of the count, whereas in the United States of America, there are 20 patients per 100,000 inhabitants, per annum. The main risk group is that of over 60 year-old men, who present comorbidities such as obesity, smoking and diabetes [69-71].

Its pathology includes the drop in the amount of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) and by the grouping of a-synuclein proteins in form B, observed in inclusions between cells, called Lews Bodies (LB) [72,73]. In regards to a cause there is no single consensus, the most acceptable theory is that Parkinson's occurs at a junction of factors, such as genetic, environmental and immune ones, leading to mitochondrial changes and oxidative stress as potentiating these neurons death [74]. Symptoms can be motor, such as tremor even at rest and muscle hardness; added to non-motor ones, such as problems with smell, impaired vision, cognitive changes, weakness of bones and psychiatric disorders, such as depression; most of the time it leads to death in an interval of 7 to 14 years in more severe cases [75-78].

Although there is no concrete evidence for the functioning of oxidative stress in the disease process, research shows that because it provides most of the oxygen, when mitochondria have problems in the complex of producing redox reactions in the energy process, there is a possibility of an increase in reactive oxygen strains as peroxides and superoxides; thus, they wind up suffering from oxidative stress.

The latter, which may be one of the factors responsible for the cell death of dopamine neurons, in addition to mutations when they affect the DNA, promotes this loss of cells. In addition, oxidative changes in DNA, proteins and lipids were also found in patients' brain tissues; oxidative stress comprises more, neuroinflammation [79,80].

Generally, current treatment is done through dopaminergic drugs, in order to correct motor changes, where levadopa is the most common one [81]. Some plants were tested as a potential phytotherapic for treating the disease, by verifying their antioxidant, anti-inflammatory and anti-apoptic action. A significant part of these effects is due to polyphenols [82]. The use of *Guazuma ulmifolia* as a phytotherapy for the treatment of this disease, was not found in the scientific literature, however, as it has a representative antioxidant ability, mainly in its leaves, it may become, the target of further studies.

Leaves hold a large amount of flavonoids and alkaloids and bear the ability to stop the production of lipid peroxides [83]. This plant's leaf and bark also hold quercetin, a flavonoid that has the potential to fight neurodegenerative diseases, such as Parkinson's [84,85]. Therefore, the Amazon biome, which represents one of the highest biodiversities in the world, presents a paucity of studies addressing the sustainable extraction of plant resources, which can contribute to the elaboration of effective medicines or phytterapics, to be employed on the treatment of, degenerative diseases [86]. Given this study, it was found that the popular use of riverside populations and the interior of the municipalities of Manaus-AM, Brazil, in addition to results of physical-chemical studies [87] and with animals [84], can be promising when future studies are carried out with human beings to warrant their action in improving the biochemical, hormonal and neural parameters of neurodegenerative diseases.

Conclusion

Guazuma ulmifolia is one of the plants with phytotherapeutic potential for chronic non-communicable diseases, with great prospects for the protection of neurodegenerative diseases, due to the presence of phytochemicals, such as polyphenols, flavonoids, alkaloids and tannins in its chemical constitution, which are essential in anti-inflammatory and antioxidant activities. It was also ascertained there to be no reports of any analyses on bioactive plants, which had been used in humans, just in rats, *in vitro* or *in vivo*, therefore further studies show to be needed to define their therapeutic ability in humans.

Author's Contribution

All authors were involved in the writing and review of the paper.

Disclosure Statement

No conflicts of interest declare by the authors.

Data Availability Statement

Data sharing not applicable- no new data generated. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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