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Article

Phytocomponents, Evaluation of Anticholinesterase Activity and Toxicity of Hydroethanolic Extracts of *Parkia platycephala* Benth.

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This study evaluated the chemical composition, antioxidant and anticholinesterase activities, and the toxicity of hydroethanolic extracts of the *Parkia platycephala* Benth. Hot extraction with 70% hydroethanolic solution was used to obtain crude extracts of the leaf (LE), bark (BE), flower (FE), and seed (SE). Separation and identification of the compounds were performed by liquid chromatography with diode array detection and gas chromatography coupled with mass spectrometry. Antioxidant and anticholinesterase activities were performed by the 2,2-diphenyl-1-picrylhydrazyl (DPPH•) and Ellman methods, respectively, and the preliminary toxicity by the method with *Artemia salina*. Chromatography analysis indicated naringin, kaempferol, stigmasterol, and β-sitosterol in all extracts. Gallic acid is prominent in the LE and FE, while ferulic acid is abundant in the BE and lupeol and lupeol acetate are prominent in the SE. The BE antioxidant activity (lethal concentration of 50% (IC_{50}) = 14.72 ± 0.13 μg mL^{-1}) is equivalent to the standard rutin (IC_{50} = 15.85 ± 0.08 μg mL^{-1}). The SE had the best acetylcholinesterase inhibition potential (IC_{50} = 5.73 ± 0.68 μg mL^{-1}). Aside from the SE, which is not toxic, the other extracts had low (LE, FE) and moderate (BE) toxicity. The extracts of *P. platycephala* have potential antioxidant and therapeutic uses, especially against Alzheimer's disease.

Keywords: Alzheimer, antioxidant potential, Cerrado, chemical characterization, fava de bolota

Introduction

The tropical savannah (Cerrado) covers a large area of Brazil and is frequently defined by vegetation that is resistant to adverse edaphoclimatic conditions. Despite representing the largest flora among the savannas in the world,[1] only 8.21% is still in a state of nature conservation.[2]

The region has a substantial agricultural sector (approximately 17.43 Mha of soybean, corn, and cotton grains in 2014) which has degraded much of its native cover, affecting the carbon stock and biodiversity of this biome.[3-6]

Due to its location on the border of the Amazon and Caatinga biomes, its biodiversity is diverse, with only 30% of plants catalogued.[1] Despite their low ethnobotanical indexes, these plants are widely used for therapeutic purposes,[7] leading to indiscriminate exploitation as a result of predatory extractive actions and permissive conservation policies.[8]

Bioprospecting plant species is a tool for designing conservation strategies for native species that promotes sustainable regional development by elucidating the social,

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economic, cultural and environmental value of medicinal plants.[9] Additionally, it establishes new possibilities for combining social constructivism and realism in studies of political ecology.[10]

The species *Parkia platycephala* Benth., also known as "*fava de bolota*", "*faveira*" or "*visgueira*", belongs to the Mimosaceae family (subfamily Mimosoideae or Leguminosae II) and is an endemic plant found in the Brazilian states of Tocantins, Maranhão and Piauí.[11,12]

In vivo tests have proven some pharmacological activities of this species, such as the antinociceptive, anti-inflammatory, gastroprotective and anthelmintic effects of lectin purified from *P. platycephala* Benth. seed extracts.[13,14] Most of the scientific studies on *P. platycephala* Benth. make reference to pods and their use in cattle nutrition and gastrointestinal infections.[15-17]

The *Parkia* genus is quite numerous. However, little is known about the chemistry of its species.[18] This genus has been found to contain phenolic acids,[19] flavonoids,[20] terpenoids,[21,22] steroids,[23] tannins[24] and fatty acids.[25] These compounds are effective in the treatment of Alzheimer's disease.[17]

Patients with Alzheimer's disease do not synthesize acetylcholine (ACh), an essential substance in neuronal activity. Acetylcholinesterase (AChE) inhibitors are currently believed to improve disease-related dementia symptoms.[26] *In vitro* and *in vivo* studies of acetylcholinesterase inhibition (iAChE) suggest that the Cerrado species are promising sources of therapeutic compounds against Alzheimer's disease.[27-29]

The evaluation of the antioxidant capacity of the *Parkia* genus is mentioned in some studies.[18] However, the analysis of the neuroprotective potential, such as the inhibition of acetylcholinesterase, is limited. Additionally, concerns about the toxicity of its species are scarce, even with pharmacological activities in amplification process.

Thus, the purpose of this work was to conduct phytochemical bioprospecting and to investigate the antioxidant and anticholinesterase properties, as well as the toxicity of *Parkia platycephala* Benth. extracts.

Experimental

Collection and preparation

The leaf, bark, flower, and seed samples of *Parkia platycephala* Benth. were collected in Palmas-TO, at the Federal University of Tocantins (UFT), Palmas Campus (10°10'55"S and 48°21'45"W) and were registered an incorporated into the collection of the Herbarium of the UFT under number HTO 12007 and the project was also registered with National Genetic Heritage Management System (SisGen) under number A06B860. The samples were dried (60 ºC/48 h) and sprayed (knife mill) and then stored in closed glass bottles in a light-free environment.

Extraction

The hot extractive method in a closed system using Soxhlet equipment was used to obtain crude hydroethanolic extracts of the leaf (LE), bark (BE), flower (FE) and seed (SE). The proportion of 5 g of vegetable powder to 200 mL of 70% ethanol solution (polar extraction) was used for approximately 5 h of reflux. After the extraction, the solvent was removed using a rotary evaporator (FISATOM, São Paulo, Brazil) at 600 mmHg at 45 ºC, then the extracts were frozen at −70 ºC and then lyophilized in a LIOTOP L101 (São Carlos, Brazil) lyophilizer.

Characterization by liquid chromatography with diode array detection (LC-DAD)

The extracts were solubilized in water:methanol (8:2; v:v) and evaluated on an LC analytical column (LC-6AD Shimadzu, Kyoto, Japan) with the aid of a photodiode detector system (PDA) which was monitored between the wavelengths λ = 200-800 nm. In an LC analytical apparatus, the column was ODS HYPERSIL (C18, 4.6 × 150 mm in diameter, Thermo Electron Corporation, Waltham, USA). The injection flow and volume were, respectively, 1 mL min^{-1} and 10 µL. All chromatographic analyses took place at a temperature of 25 ºC. The eluent A was composed of a binary mobile phase of water with acetic acid (6%) and sodium acetate (2 mM), and the eluent B, composed of acetonitrile and the following gradient was applied: 0 min 5% B; 20 min 15% B; 30 min 60% B; and 40 min 100% B. Caffeic acid, ellagic acid, ferulic acid, gallic acid, naringin and kaempferol standards were used (98%, Sigma, St. Louis, MO, USA), prepared in methanol-water at a concentration of 1,000 µg mL^{-1}. The identification of compounds with the aid of a PDA scanning detector in the spectral range of 200-800 nm did not reveal any interference in the retention time of the samples in LC by the developed elution method. Standards were easily identified and quantified based on their absorption spectra in the UV region and retention time. The patterns found in the extracts were unequivocally identified by performing co-injection experiments in which aliquots of the extracts and standards were mixed and diluted to a known volume and analyzed by LC. Calibration curves were determined by linear regression using LC. The linearity of the standards was evaluated for 10 concentration ranges. The standard

errors of the mean for peak areas of replicate injections (n = 5) were less than 2%, showing good repeatability of the calibration curve. The limit of detection was determined by injecting (n = 5) solutions of thiamethoxam of known concentration (20 µL each) and then decreasing the concentrations of the samples until detection of a peak with a signal/noise ratio of 3 (Table S1, Supplementary Information (SI) section). Analyses were performed in quintuplicate.

Characterization by gas chromatography coupled to mass spectrometry (GC-MS)

GC-MS analysis was performed using a GC-2010 Plus, Shimadzu, Kyoto, Japan, equipped with a mass spectrometry detector (GC-MS Ultra 2010), using LM-5 (5% phenyldimethylpolysiloxane), capillary column of fused silica (0.2 mm × 15 m internal diameter and 0.2 µm thick film). 100 mg of the extract was weighed, then 2.0 mL of water and 2.0 mL of hexane were added. After the formation of the phase, the hexane fraction was separated from the aqueous fraction. To the aqueous fraction, 2 mL of hexane was added, and the process was repeated. After the two extractions, the hexane fractions were dried and suspended in 1,000 mL of hexane. For GC-MS analysis, the solution was first filtered through a 0.45 µm ultrafilter (Millex® syringe filter units, disposable, diameter 13 mm, polytetrafluoroethylene (PTFE) membrane, Fluoropore). The analysis took place under the following conditions: helium carrier gas (99.999% and flow rate of 1.0 mL min^{-1}), 1.0 µL injection volume, ratio of division (1:20), initial oven temperature set at 150 ºC and heating at 150 to 280 ºC, at 15 ºC min^{-1}, and one hold at 280 °C for 15 min.[30] The injector temperature was 280 °C and the quadrupole detector temperature was 280 °C. The MS scan parameters included an electron impact ionization voltage of 70 eV, a mass range of 45-600 nm (*m/z*) and a scan interval of 0.3 s. The identifications were performed by comparing the mass spectra obtained from the NIST21 and WILEY229 libraries. In some cases, when the identified spectra were not found, only the structural type of the corresponding component was proposed based on its mass spectral fragmentation. When possible, reference compounds were co-chromatographed to confirm GC retention times. Stigmasterol, β-sitosterol, lupeol and lupeol acetate (Sigma, ≥ 98%, St. Louis, MO, USA) standards were prepared in hexane at a concentration of 1,000 µg mL^{-1} and the spectrum obtained from each standard were shown in Figures S3-S7 (SI section). Compound concentrations were determined by external calibration. Linearity for the standards was assessed for 5 concentration ranges. Linearity for the standards was assessed for 5 concentration ranges. The standard errors of the peak areas of replicate injections (n = 5) were less than 2%, thus showing good repeatability of the calibration curve. The respective coefficients of determination (r^2) were 0.9996 for stigmasterol, kaempferol, β-sitosterol and lupeol, and r^2 = 0.9994 for lupeol acetate. Analyses were performed in quintuplicate.

Determination of antioxidant activity

The antioxidant power was measured by the elimination of the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH•) method, following the descriptions by Brand-Williams *et al.*[31] and with some modifications, according to Fernandes *et al.*[32] The lethal concentration of 50% (IC_{50} / (µg mL^{-1})) was determined from the Graphpad Prism 9.0.0 program by non-linear regression,[33] denoting the concentration of a sample necessary to decrease the absorbance by 50% at 517 nm.

Anticholinesterase activity determination

The inhibitory activity of the enzyme acetylcholinesterase (iAChE) was determined based on the method described by Ellman *et al.*,[34] which used 96-well plates and a final concentration of 0.2 mg mL^{-1}, to measure the absorbance at 405 nm (Elisa BIOTEK, modelo ELX 800, software Gen5 V2.04.11) for 30 s. Then, the enzyme acetylcholinesterase (0.25 U mL^{-1}) was incubated and absorbance was measured for 25 min, at intervals of 1 min. All samples were analyzed in triplicate. Physostigmine was used as a positive control. The IC_{50} was determined from the Graphpad Prism 9.0.0 program[33] by non-linear regression.

Toxicity determination

The preliminary analysis of the toxic potential was carried out using the *Artemia salina* (*A. salina*) according to the methodology of Meyer *et al.*,[35] with adaptations. Initially, the eggs of *A. salina* (0.1 g) were incubated in 1 L of saline solution at 3%, with synthetic sea salt, pH adjusted between 8 and 9 (with 1 M sodium carbonate), exposed to artificial light (incandescent lamp 60 W) for 24 h for the hatch to occur.

Test tubes were prepared in triplicate, with 5 mL of extract solution (LE, BE, FE, SE) diluted in dimethyl sulfoxide (DMSO) saline solution (1%), in varying concentrations (0; 4; 250; 1,000; 4,000 µg mL^{-1}) and also tubes containing only DMSO solution (1%) diluted in saline solution (3%) for the control group, all with pH

adjusted between 8 and 9. Then, 10 nauplii were added to each test tube. After 24 h, the number of immobile nauplii was counted and the percentage of mortality was determined, from which the IC_{50} of each extract was determined from the Graphpad Prism 9 program by non-linear regression.[33] The classification of the extract followed the criteria established by Nguta *et al.*,[36] who define extracts with IC_{50} values < 100 μg mL^{-1} as highly toxic, 100 μg mL^{-1} < IC_{50} < 500 μg mL^{-1}, moderately toxic, 500 μg mL^{-1} < IC_{50} < 1,000 μg mL^{-1}, as having low toxicity and IC_{50} > 1,000 μg mL^{-1} as non-toxic.

Statistical analysis

The content of chemical characterization, antioxidant activity and anticholinesterase activity are presented as mean ± standard deviation (SD) of the determination in quintuplicates and triplicates, respectively. Analysis of variance (ANOVA) and Tukey's test were used to identify significant differences between means ($p < 0.05$).

Results and Discussion

Characterization by LC-DAD

In the analysis by LC-DAD of the extracts of the leaf, bark, flower and seed of *P. platycephala* Benth. the phenolic acids (gallic, ellagic, caffeic and ferulic), the flavonone naringin and the flavonol kaempferol were identified and quantified (Table 1) and the chromatograms obtained from the extracts are shown in Figure S1 (SI section).

Table 1. Contents of chemical compounds using LC-DAD in the crude hydroethanolic extracts of the leaf (LE), bark (BE), flower (FE) and seed (SE)

Compound	Concentration / (mg g^{-1})			
	LE	BE	FE	SE
Gallic acid	217.6 ± 1.1[a]	159.4 ± 0.9[b]	192.9 ± 1.1[c]	–
Caffeic acid	174.6 ± 1.2[a]	119.7 ± 0.7[b]	–	–
Ferulic acid	107.9 ± 1.0[b]	182.7 ± 1.0[a]	–	–
Ellagic acid	182.1 ± 0.7[a]	–	123.4 ± 1.0[b]	–
Naringin	84.8 ± 0.4[a]	77.3 ± 0.2[b]	65.9 ± 0.5[d]	75.1 ± 0.4[c]
Kaempferol	98.7 ± 0.2[a]	87.6 ± 0.5[b]	79.2 ± 0.3[c]	87.2 ± 0.2[b]

Values represent the mean, followed by the standard deviation (mean ± SD). Different letters, in the same line, mean statistically different results from each other by the Tukey's test ($p < 0.05$).

Naringin and kaempferol were found in all extracts, emphasizing the LE with significant quantities of both. For kaempferol, there was also a statistical resemblance between BE and SE. The main contents of gallic acid in the LE (217.6 ± 1.1 mg g^{-1}) and FE (192.9 ± 1.1 mg g^{-1}) stand out, as do ferulic acid in the BE (182.7 ± 1.0 mg g^{-1}) and ellagic acid in the LE (182.1 ± 0.7 mg g^{-1}).

The chemical characterization of the species *P. platycephala* Benth. is still poorly described, although there are studies with the genus *Parkia* that may indicate possible common compounds. Gallic and ellagic acids, naringin, and kaempferol have already been identified in studies using the ethanol extract of the *P. platycephala* Benth. leaf.[37]

Caffeic and ferulic acids are present in the pods of the species *Parkia speciosa* Hassk. and *Parkia javanica* (Lam.) Merr.[38,39] These compounds inhibit the production of gastric acid secretion,[40] generating a gastroprotective effect. Such bioactivity was proven in the leaves of the species *P. platycephala* Benth.[14]

Notably, gallic acid has strong anti-inflammatory activity in neurodegenerative diseases, being able to reverse scopolamine-induced amnesia because of its capacity to inhibit oxidative stress. It also acts to decrease the activity of acetylcholinesterase.[41]

Ellagic acid generates neuroprotective effects and cognitive improvement, which are achieved by the reduction in oxidative stress.[42] Kaempferol relieves memory impairment, reduces neuroinflammation, and may be indicated as an agent against Parkinson's disease, Alzheimer's disease and cerebral ischemia.[43,44]

Another potential neuroprotective agent is naringin. Studies[45,46] show that the compound causes the suppression of acetylcholinesterase activity in rats, as well as the increased expression of the neurotrophic factor and the reduction of seizures.

Characterization by GC-MS

In the GC-MS analysis, five compounds were identified and quantified, of which three are steroids (campesterol, stigmasterol and β-sitosterol) and two triterpenoids (lupeol and lupeol acetate) (Table 2). The representative chromatogram from the extracts is shown in Figure S2 (SI section).

The β-sitosterol content was major in LE (61.3 ± 0.2 mg g^{-1}) followed by BE (60.1 ± 0.2 mg g^{-1}) when all extracts were compared. Regarding lupeol (71.8 ± 0.3 mg g^{-1}), lupeol acetate (55.5 ± 0.2 mg g^{-1}) and stigmasterol (34.3 ± 0.1 mg g^{-1}), SE showed statistically higher levels than the other extracts.

Although most reports on the characterization of the genus *Parkia* are from pods or seeds, there is some information available on leaves and bark.[18] Some studies[18] of species in this genus also identified the compounds of

Table 2. Contents of chemical compounds quantified by GC-MS in crude hydroethanolic extracts of the leaf (LE), bark (BE), flower (FE) and seed (SE) of *P. platycephala* Benth.

Compound	Concentration / (mg g^{-1})			
	LE	BE	FE	SE
Campesterol	21.0 ± 0.1[a]	20.7 ± 0.1[b]	–	18.9 ± 0.1[c]
Stigmasterol	25.3 ± 0.1[c]	25.7 ± 0.2[b]	24.7 ± 0.1[d]	34.3 ± 0.1[a]
β-Sitosterol	61.3 ± 0.2[a]	60.1 ± 0.2[b]	22.1 ± 0.1[d]	23.7 ± 0.2[c]
Lupeol	49.5 ± 0.2[b]	48.4 ± 0.1[c]	–	71.8 ± 0.3[a]
Lupeol acetate	51.9 ± 0.2[c]	52.7 ± 0.2[b]	–	55.5 ± 0.2[a]

Values represent the mean, followed by the standard deviation (mean ± SD). Different letters, in the same line, mean statistically different results from each other by the Tukey's test ($p < 0.05$).

this research. The species *Parkia speciosa* Hassk. presents campesterol, stigmasterol, β-sitosterol and lupeol in its seeds.[25] In the species *Parkia biglobosa* (Jacq.) G.Don (*P. biglobosa*) campesterol, stigmasterol and β-sitosterol (seeds), lupeol (bark) and lupeol acetate (leaves and bark) were detected.[47-49] It was also verified β-sitosterol in the leaves of *Parkia javanica* auct.[50] There are reports of the presence of β-sitosterol (bark) and lupeol (root) in the species *Parkia bicolor*.[51,52]

Lupeol is a natural triterpene with proven anti-inflammatory and immunomodulatory actions that act directly on the brain, inducing neuroprotection.[53] Lupeol acetate has been shown to be neuroprotective because of the anti-inflammatory activity that it acts on brain opioids.[54] According to Wang *et al.*,[55] this effect is beneficial for treating Alzheimer's disease.

Ayaz *et al.*[56] state that β-sitosterol has double efficiency as it inhibits the acetylcholinesterase enzyme and eliminates free radicals in the brain. These effects consequently improve cognitive deficits, short-term memory and locomotor impairments.[57]

Antioxidant and anticholinesterase activities

High antioxidant potentials, $IC_{50} < 3 \times IC_{50\ [rutin]}$,[57] and iAChE ($IC_{50} < 20$ μg mL^{-1})[17] were determined in the crude extracts of the leaves, bark, flowers and seeds of *P. platycephala* Benth. (Table 3).

The antioxidant activity of the BE (IC_{50} = 14.72 ± 0.13 μg mL^{-1}) is statistically equivalent to the activity of the positive control, rutin (IC_{50} = 15.85 ± 0.08 μg mL^{-1}). Studies performed with the bark of the species *P. biglobosa* confirm its excellent antioxidant potential (DPPH•, IC_{50} = 6.210 ± 0.001 μg mL^{-1}).[58] Among the phenolic compounds detected in the BE, ferulic acid, which constitutes the majority of this extract, has been widely studied because of its high antioxidant potential.[59]

Table 3. Antioxidant potential and acetylcholinesterase activity of crude hydroethanolic extracts of the leaf (LE), bark (BE), flower (FE) and seed (SE) of *Parkia platycephala* Benth. and the control rutin (R) and physostigmine (P)

Extract	DPPH• IC_{50} / (μg mL^{-1})	iAChE IC_{50} / (μg mL^{-1})
LE	29.32 ± 1.00[b]	13.07 ± 0.61[c]
BE	14.72 ± 0.13[a]	13.02 ± 0.15[c]
FE	35.45 ± 1.36[c]	12.73 ± 0.73[c]
SE	ND	5.73 ± 0.68[b]
R	15.85 ± 0.08[a]	–
P	–	1.15 ± 0.05[a]

Values represent the mean followed by the standard deviation (mean ± SD). Different letters, in the same column, mean statistically different results from each other by the Tukey's test ($p < 0.05$). IC_{50}: lethal concentration of 50%; ND: not detected; DPPH: 2,2-diphenyl 1-picrylhydrazyl; iAChE: acetylcholinesterase inhibition.

It is easily absorbed by the body and has the ability to stay in the blood for a long time.[60]

Recent studies[31] with the leaves and seeds of *P. platycephala* Benth. demonstrated that the sequential extraction with increasing polarity (hexane, methanol, and ethanol 70%), was promising for the leaf extracts, presenting relevant antioxidant potential (DPPH•), both for the methanolic extract (IC_{50} = 30.19 ± 0.75 μg mL^{-1}) and the hydroethanolic extract (IC_{50} = 40.62 ± 0.65 μg mL^{-1}). However, the antioxidant potential of the LE (IC_{50} = 29.32 ± 1.00 μg mL^{-1}) suggests that the polar extraction method optimized the extraction process, as it increases the antioxidant capacity of the hydroethanolic extract. The extraction method had no effect on the antioxidant capacity of the seed extracts, as neither reached 50% of the tested concentrations (10-200 μg mL^{-1}).[31] According to Farias *et al.*,[61] the antioxidant activity of *P. platycephala* Benth. seed extract is of low potential, which can be explained by its absence of phenolic acids.

In the studies performed by Dubey *et al.*,[62] the leaf and flower extracts of the *Parkia roxburghii* G.Don species presented an antioxidant potential (DPPH•) of IC_{50} = 16 ± 0.002 μg mL^{-1} and IC_{50} = 68 ± 0.004 μg mL^{-1}, respectively. Comparing the species, it was found that in both, the leaves presented antioxidant power superior to the flowers, however the antioxidant potential of the leaves (IC_{50} = 35.45 ± 1.36 μg mL^{-1}) of *P. platycephala* Benth. is lower than that of potential of *Parkia roxburghii* G.Don leaf extract, while for the flowers the effect was the opposite. Such variations can be explained by species differentiation and edaphoclimatic conditions. Both of these factors have a direct impact on the metabolite composition of the plant.[63]

Regarding the iAChE effect, as shown in Table 3, it was observed that the SE (IC_{50} = 5.73 ± 0.68 μg mL^{-1}) is the most

potent extract. The other extracts are statistically similar and also have a high inhibitory potential. This bioactivity is confirmed by Fernandes *et al*.[32]

When performing the comparison between extractive methods polar extraction and sequential extraction with increasing polarity, from the leaf and seed of *P. platycephala* Benth., it was observed their influence on the inhibitory effect of acetylcholinesterase, only in the seed extracts, with the polar extraction having a better efficiency (IC_{50} = 5.73 ± 0.68 μg mL^{-1}), while the sequential extraction with increasing polarity presented IC_{50} = 9.85 ± 0.76, 12.14 ± 0.12 and 12.90 ± 0.14 μg mL^{-1}, for the hexane, methanolic and hydroethanolic extracts, respectively.[32]

The excellent effect of SE was associated with the compounds lupeol (71.8 ± 0.31 mg g^{-1}) and lupeol acetate (55.5 ± 0.2 mg g^{-1}). Ahmad *et al*.[64] performed *in vivo* tests in mice, with an accumulation of β-amyloid plaques, one characteristic of Alzheimer's. Oral doses (50 mg kg^{-1}) of lupeol were administered to these mice. The results were a significant decrease in oxidative stress, neuroinflammation, and memory impairments.[61]

According to Nejma *et al*.,[65] lupeol has an iAChE effect (IC_{50} = 38.31 ± 1.30 μg mL^{-1}), due to the triterpene configuration and the free C-3 secondary alcohol of the compound. Its derivative, lupeol acetate, also has an acetylcholinesterase inhibitory effect (IC_{50} = 142.55 ± 2.12 μg mL^{-1}). Following the classification criteria of Santos *et al*.,[17] both are in the range of moderate effect (20 μg mL^{-1} < IC_{50} < 200 μg mL^{-1}).

It is believed that the inhibitory power of the other extracts (LE, BE and FE) is related to the association between phenolic compounds and steroids detected in each extract.

Karimi *et al*.[66] stated that even small molecules such as stigmasterol, β-sitosterol and campesterol have an inhibitory effect on acetylcholinesterase and are possible successful cases in the discovery of new anti-Alzheimer drugs.

According to Elufioye *et al*.,[67] campesterol has a high iAChE power (IC_{50} = 1.89 μg mL^{-1}), confirming the various studies that indicate phytosterols as excellent inhibitors of this enzyme.

Compounds such as gallic acid have an excellent iAChE effect (IC_{50} = 5.85 μM or 0.995 μg mL^{-1}).[68] Kaur *et al*.[69] observed the iAChE effect of ethyl acetate fractions of the *Ganoderma mediosinense* species. After purifying one of these fractions, they reported that gallic acid was responsible for this effect.[69]

Tests proved that the administration in mice of ferulic acid (10 and 20 mg kg^{-1} of body weight) associated with cadmium inhibited AChE and improved the neuromodal conditions of the animals.[70]

Caffeic acid has been proven to modulate AChE activity (*in vitro* and *in vivo*), with positive effects on cerebral circulation and cognitive performance.[71] Sabernavaei *et al*.[72] isolated caffeic acid from the methanolic fraction of the species *Leutea avicennia*. This compound showed excellent iAChE power (IC_{50} = 12.06 ± 2.01 μg mL^{-1}).

Oh *et al*.[73] isolated the ellagic acid from the species *Castanopsis cuspidata* and verified, in *in vivo* tests, that this compound has excellent iAChE power (IC_{50} = 12.6 ± 2.4 μg mL^{-1}).

Notably, no prior studies evaluating the inhibition of acetylcholinesterase by extracts of plant species from the bark and flower of the genus *Parkia* have been identified; thus, the data presented here are the first reports of the genus, specifically of the species *Parkia platycephala* Benth., indicating its potential therapeutic use against Alzheimer's disease.

Toxicity determination

Table 4 shows the toxicological results for crude extracts of the leaf, bark, flower and seed of *P. platycephala* Benth.

Table 4. Lethal concentration of 50% (IC_{50}) of hydroethanolic extracts of the leaf (LE), bark (BE), flower (FE) and seed (SE) of *P. platycephala* by test with *Artemia salina*

Extract	IC_{50} / (μg mL^{-1})	Toxicity
LE	522.37 ± 65.8	low
BE	445.00 ± 68.2	moderate
FE	772.00 ± 0.01	low
SE	ND	non toxic

ND: not detectable; values represent the mean, followed by the standard deviation (mean ± SD).

Using *P. platycephala* Benth. extracts for medicinal purposes are relatively safe, since 50% of the extracts exhibited a low-level toxicity (500 μg mL^{-1} < IC_{50} < 1,000 μg mL^{-1}), and the SE showed no toxicity (IC_{50} > 1,000 μg mL^{-1}).

Fernandes *et al*.[74] confirm the safe use of *P. platycephala* Benth. leaf extracts after verifying the absence of acute toxicity (1,000 mg kg^{-1}) and cytotoxicity in erythrocytes (100 μg mL^{-1}) of mice.

P. biglobosa leaf extract showed slight toxicity to fish at 500-5,000 mg kg^{-1} body weight.[75] The aqueous extract of *Parkia clappertoniana* Keay seed, administered orally (100-500 mg kg^{-1}) to rats, was classified as non-toxic.[18,76]

There was no evidence of cytotoxicity of *P. biglobosa* bark extract on murine C_2C_{12} muscle cells at concentrations up to 300 μg mL^{-1}.[77] However, *in vivo* oral and intraperitoneal (ip) acute toxicity tests were also conducted in adult Wistar

mice. While no deaths were observed at the maximum dose (1,000 mg kg^{-1}), some toxicity was observed following ip administration, with an IC_{50} estimated at 457 mg kg^{-1}.[77] As a result, the bark extract is classified as moderately toxic.[78]

Preliminary toxicity tests with *A. salina* were also performed by Nounagnon *et al.*[79] in ethanol extracts of the leaf and bark of *P. biglobosa* and they demonstrated a more pronounced toxicity in the bark, presenting a lethal dose equivalent to half of the leaf dose.

Finally, it is important to continue researching on the species *P. platycephala* Benth., as the data presented here suggest that it possesses promising biological activities, including antioxidant and anticholinesterase capacity.

Conclusions

The chemical composition of *P. platycephala* Benth. from Biome Cerrado in the State of Tocantins (Brazil) allowed the quantification of phenolic acids (gallic, ellagic, ferulic, caffeic acid), flavonone (naringin), flavonol (kaempferol), steroids (campesterol, stigmasterol and β-sitosterol) and triterpenoids (lupeol and lupeol acetate).

The LE, CE and FE all possessed significant antioxidant potential. The fact that all extracts of *P. platycephala* Benth. inhibit acetylcholinesterase adds to the evidence of action against Alzheimer's disease. Except for BE, which was moderately toxic in the *A. salina* model, the extracts exhibited low toxicity.

In this context, additional research with the species is recommended in order to foster local research aimed at isolating active principles and developing novel therapeutic indications.

Supplementary Information

Supplementary information (Figures S1-S6, Table S1) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

Rachel M. N. Fernandes was responsible for conceptualization, data curation, formal analysis, writing original draft, writing-review and editing; Maria Angélica M. Rodrigues for the data curation, formal analysis and validation; Claudia Andrea L. Cardoso, Daniela R. Alves and Selene M. Morais for the conceptualization, data curation and formal analysis, Juliane F. Panontin for the formal analysis and writing original draft; Elisandra Scapin for the conceptualization, funding acquisition, validation, visualization, writing original draft, writing-review and editing.

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