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Total phenolic content and antioxidant and anticholinesterase activities of medicinal plants from the State's Cocó Park (Fortaleza-CE, Brazil)

Teor de fenóis totais e atividades antioxidante e anticolinesterase de plantas medicinais do Parque Estadual do Cocó (Fortaleza-CE, Brasil)

Contenido total de fenoles y actividades antioxidantes y anticolinesterasas de plantas medicinales en el Parque Estatal Cocó (Fortaleza-CE, Brasil)

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Abstract
The State's Cocó Park in the city of Fortaleza-CE present mainly a mangrove flora and include landscape and medicinal plants. The aim of this study is determining the total phenol content, antioxidant activity against the free radical DPPH and the inhibition of the enzyme acetylcholinesterase (AChE) in ethanolic extracts of 30 medicinal plants and thus assess which plants have potential against Alzheimer's Disease. The plants rich in phenolic compounds with amounts ranging from 297.46 ± 26.94 to 599.30 ± 17.08 mg GAE/g plant extract, which showed greater antioxidant activities (with IC_{50} against DPPH radical from 3.44 ± 0.16 to 3.73 ± 0.12 µg mL^{-1}) and higher acetylcholinesterase inhibiting power (IC_{50} < 20 µg mL^{-1}) were *Anacardium occidentale, Ceiba pentandraLaguncularia racemosa, Mangifera indica, Myracrodrum urundeuva* and *Terminalia catappa*. Then, these species and their constituents are recommended for more specific studies related to Alzheimer´s Disease.
Keywords: Cocó State Park; Medicinal plants; Antioxidant activity; Anticholinesterase activity.

Resumo
O Parque Estadual do Cocó na cidade de Fortaleza-CE apresenta uma flora principalmente constituída de manguezais e inclui plantas decorativase plantas medicinais. O objetivo deste estudo é determinar o teor de fenóis totais a atividade antioxidante contra o radical livre DPPH e a inibição da enzima acetilcolinesterase (AChE) em extratos etanólicos de 30 espécies de plantas medicinais e assim avaliar quais plantas têm potencial contra a doença de Alzheimer. As plantas ricas em compostos fenólicos com teores superiores variando de 297,46 ± 26,94 a 599,30 ± 17,08 mg GAE/g extrato vegetal, que apresentaram maiores atividades antioxidantes (com IC_{50} contra o radical DPPH de 3,44 ± 0,16 a 3,73 ± 0,12 µg mL^{-1}) e poder inibidor da acetilcolinesterase (IC_{50} < 20 µg mL^{-1}) foram *Anacardium occidentale, Ceiba pentandra, Laguncularia racemosa, Mangifera indica, Myracrodrum urundeuva e Terminalia catappa*. Então, essas espécies e seus constituintes são recomendados para estudos mais específicos relacionados à Doença de Alzheimer.

Palavras-chave: Parque Estadual do Cocó; Plantas medicinais; Atividade antioxidante; Atividade anticolinesterásica.

Resumen
El Parque Cocó del Estado en la ciudad de Fortaleza-CE presenta principalmente una flora de manglar e incluye plantas paisajísticas y medicinales. El objetivo de este estudio es determinar el contenido total de fenol, la actividad antioxidante frente al radical libre DPPH y la inhibición de la enzima acetilcolinesterasa (AChE) en extractos etanólicos de 30 especies medicinales y así evaluar qué plantas tienen potencial contra la enfermedad de Alzheimer. Las plantas ricas en compuestos fenólicos con cantidades que van desde 297.46 ± 26.94 a 599.30 ± 17.08 mg GAE/g de extracto vegetal, que mostraron mayor actividad antioxidante (con IC_{50} contra el radical DPPH de 3.44 ± 0.16 a 3.73 ± 0.12 µg mL^{-1}) y superiores El poder inhibidor de la acetilcolinesterasa (IC_{50} < 20 µg mL^{-1}) fueron *Anacardium occidentale*, *Ceiba pentandra*, *Lagucularia racemosa*, *Mangifera indica*, *Myracrodrum urundeuva y Terminalia catappa*. Luego, estas especies y sus constituyentes se recomiendan para estudios más específicos relacionados con la enfermedad de Alzheimer.
Palabras clave: Parque Estatal Cocó; Plantas medicinales; Actividad antioxidante; Actividad anticolinesterasa.

1. Introduction

The park bordering the Cocó river occupies an environmental conservation area containing 1,571.29 hectares, making it the largest natural park in an urban area in North/Northeast Brazil and the fourth in Latin America. Consisting mainly of mangroves, the park is a haven for the city's fauna. Being considered a kind of natural nursery for mollusks, crustaceans, fish, reptiles, birds and mammals, mainly *Callithrix jacchus* (Sousa & Santos, 2016)). The State's Cocó Park besides offering leisure and tourist attractions, gives the opportunity for the elaboration of scientific researches.

Oxidative stress is an imbalance of free radicals and antioxidants in the body, which occurs naturally and plays a role in the aging process and it is related to many diseases such as cardiovascular diseases, acute and chronic kidney disease, neurodegenerative diseases, macular degeneration, biliary diseases, and cancer. There is a close relationship between oxidative stress, inflammation, and aging (Liguori et al., 2018). Oxidative stress is involved in the development of several human pathologies, such as hypertension, atherosclerosis, asthma, cancer, rheumatoid arthritis, cataracts, diabetes mellitus and degenerative diseases (sclerosis multiplies, Parkinson's disease and Alzheimer's disease) (Phaniendra et al, 2015). There is a lower incidence of degenerative diseases in populations that use diets composed of cereals, fruits, vegetables and natural foods, which are rich in antioxidant compounds, the most common being found are phenolic acids, flavonoids, vitamin C, vitamin E, selenium and carotenoids (Falco et al., 2016). Several studies have linked plant antioxidants with AChE inhibition and thus opened up several treatment options for AD (Akram & Nawaz, 2017; Penido et al, 2017).

Drugs that have AChE inhibition as a mechanism of action are called anticholinesterase or indirectly cholinergics. AChE when blocked is unable to hydrolyze ACh, thus, this neurotransmitter tends to remain active for a longer period in the synaptic cleft, a fact that increases cholinergic transmission. Drugs that block AChE in the peripheral nervous system (PNS), such as neostigmine, are used in atonic constipation, intestinal atony, urinary retention, myasthenia gravis and as an antagonist for myorelaxants. If the AChE inhibitor has an action in the central nervous system (CNS), such as Rivastigmine, it is useful in the treatment of dementia associated with Alzheimer's and Parkinson's diseases (Araujo et al., 2016).

Medicinal plants are relatively safe compared to synthetic drugs, according to the World Health Organization (WHO) it is estimated that about 80% of people worldwide depend on herbal medicines. These drugs are even used to treat neurological disorders associated with AChE regulation (Patel et al, 2018). Thus, this study aims to determine the total phenolic content, antioxidant activity and the inhibition of the enzyme acetylcholinesterase of medicinal plants present in the State's Cocó Park in Fortaleza, Ceará and elaborate a bibliographic survey on the activities reported for plants, to try to correlate with the activities determined in order to discover new herbal agents with potential to be used in the treatment of AD.

2. Methodology

Plant extracts

The collection of plant material was carried out at State's Cocó Park in Fortaleza-CE in 2018 and the samples were from specific parts of each plant species according to popular use. All samples were placed in plastic bags and transported to the Laboratory of Chemistry of Natural Products at the State University of Ceará (UECE) where exsiccates were prepared, following the botanical criteria of drying and cataloging (Matos, 1988), then they were deposited in the Prisco Bezerra herbarium of the Federal University of Ceará (UFC) with exsiccate numbers shown in Table 1.

Table 1. Plant species, exsiccate numbers, coordinates and part used.

Plants	Exsiccate	Coordinators WGS84	Used part
Anacardium occidentale	EAC 63659	Lat.: -3.74486, Long.: -38.48616	Stem bark
Annona glabra	EAC 62371	Lat.: -3,74790, Long.: -38.48692	Leaves
Bauhinia forficata	EAC 64239	Lat.: -3.74429, Long.: -38.48700	Leaves
Brosimum gaudichaudii	EAC 32315	Lat.: -3.74404, Long.: -38,48760	Stem bark
Caesalpinia pulcherrima	EAC 62367	Lat.: -3.74408, Long.: -38.48754	Leaves
Cecropia pachistacia	EAC 38591	Lat.: -3.74541, Long.: -38.48837	Leaves
Ceiba pentandra	EAC 63664	Lat.: -3.74420, Long.: -38.48674	Stem bark
Cenostigma piramidale	EAC 62700	Lat.: -3.74495, Long.: -38.48497	Leaves
Cordia oncocalyx	EAC 63021	Lat.: -3.74454, Long.: -38.48732	Stem bark
Couroupita guianensis	EAC 62686	Lat.: -3.74461, Long.: -38.48694	Leaves
Crateva tapia	EAC 63060	Lat.: -3.74541, Long.: -38.48837	Leaves
Erythrina velutina	EAC 63666	Lat.: -3.74403, Long.: -38.48686	Leaves
Genipa americana	EAC 38580	Lat.: -3.74627, Long.: -38.48848	Leaves
Geoffroea spinosa	EAC 64414	Lat.: -3.74994, Long.: -38.48473	Leaves
Guazuma ulmifolia	EAC 62729	Lat.: -3.74398, Long.: -38.48601	Leaves
Handroanthus imperginosus	EAC 63062	Lat.: -3.74514, Long.: -38.48586	Stem bark
Hymenaea stigonocarpa	EAC 63406	Lat.: -3.74501, Long.: -38.48594	Stem bark
Laguncularia racemosa	EAC 38597	Lat.: -3.74870, Long.: -38.48467	Leaves
Libidibia ferrea	EAC 63016	Lat.: -3.74402, Long.: -38.48685	Fruit
Mangifera indica	EAC 63407	Lat.: -3.74521, Long.: -38.48544	Leaves
Mimosa tenuiflora	EAC 63667	Lat.: -3.74413, Long.: -38.48737	Stem bark
Moringa oleifera	EAC 62368	Lat.: -3.74394, Long.: -38.48672	Leaves
Myracrodruon urundueva	EAC 62695	Lat.: -3.74426, Long.: -38.48664	Stem bark
Spondias mombim	EAC 63061	Lat.: -3.74474, Long.: -38.48680	Leaves
Syzygium cumini	EAC 63665	Lat.: -3.74738, Long.: -38.48745	Leaves
Talisia esculenta	EAC 64242	Lat.: -3.74548, Long.: -38.48396	Seeds
Tapirira guianensis	EAC 64238	Lat.: -3.74462, Long.: -38.48782	Leaves
Terminalia catappa	EAC 63657	Lat.: -3.74786, Long.: -38.48496	Leaves
Tocoyena formosa	EAC 64413	Lat.: -3.74425, Long.: -38.48655	Leaves
Ziziphus joazeiro	EAC 64241	Lat.: -3.74744, Long.: -38.48844	Leaves

Source: Authors.

A license to do the collection of plants from the Cocó Park was given by Secretary of the Environment of the State Government of Ceará.

To obtain the ethanol extracts, 50 grams of dry sample (oven at 60 ºC) were added to glass vessels containing 200 mL of ethyl alcohol (96%). The samples were left for 10 days, then the resulting solution was filtered and concentrated on a rotary evaporator under pressure at 60 °C to evaporate the ethanol, then placed in a water bath to dry completely.

Total phenol content

The determination of the total phenol content was carried out using the Folin-Ciocalteu method described by Sousa et al. (2007). For each extract, 7.5 mg was dissolved in 10 mL of P.A. methanol (99.8%) using an ultrasonic bath, then transferred quantitatively to a 25 mL volumetric flask and the final volume was made up with methanol. A 100 µL aliquot of this solution was transferred to a 10 mL volumetric flask with 500 µL of the Folin-Ciocalteu reagent and stirred for 30 seconds, 6 mL of distilled water and 2 mL of Na_2CO_3 (15%) were added, stirring the mixture for more 60 seconds and the final volume was filled with distilled H_2O, the solution was kept at rest for 2 hours in a dark place. The white reagent was conducted under the same conditions. All determinations were made in triplicate. The same procedure was used to prepare the calibration standard curve ($y = 0,127x + 0,011$, $R^2 = 0,995$) obtained with 0 a 4 µg. mL^{-1} gallic acid solutions. The absorbances from the several concentrations were obtained in the UV-Vis (Genesys 10S UV-Vis Thermo Scientic) at 750 nm. The results were determined by interpolation of the data with the gallic acid calibration standard equation and expressed in terms of mg GAE/g sample extract.

Determination of antioxidant activity

The determination of antioxidant capacity was carried out according to the free radical DPPH (2,2 diphenyl-1-pricryl-hydrazil) methodology proposed by Yepez et al. (2002), with some modifications. A $6.5x10^{-5}$ mol L^{-1} DPPH methanolic solution was prepared by diluting 1.3 mg of radical in 50 mL of methanol PA (Neon 99.8%) in a volumetric flask. Then, the DPPH solution was read and corrected to have a wavelength between 0.600 and 0.700 nm. The extracts were initially solubilized to prepare a stock solution with a concentration of 10,000 ppm (15 mg of the extract in 1.5 mL of methanol), afterwards, the stock solution was diluted in the respective concentrations of 5,000, 1,000, 500, 100, 50, 10 and 5 ppm. After dilutions, 1.9 mL of the $6.5x10^{-5}$ mol L^{-1} DPPH solution and 0.1 mL of the sample solution from each dilution were placed in test tubes to react. For the positive control, quercetin was used in the same concentrations and the negative control consisted of 0.1 mL of methanol with 1.9 mL of the DPPH solution. The test was maintained in the absence of light for 30 minutes and then the reading was performed on the UV-Vis spectrophotometer (Genesys 10S UV-Vis Thermo Scientic), at a wavelength of 515 nm. All procedures were performed in triplicate. The percentage of DPPH free radical inhibition by extracts at different concentrations was calculated by expressing the scavenging index percentage (IV%): $SI\% = (Abs_{DPPH} - Abs_{Amostra} / Abs_{DPPH}) \times 100$.

The effective concentration to inhibit 50% of the free radical DPPH (CE_{50}) was obtained with the aid of the Excel 2019 software, using the sample concentration values and the scavenging index (SI%). Dispersion graphs were generated whose linear equations were used to obtain the values of the mean and standard deviation. For comparison purposes, a calibration curve was constructed with different percentages of the quercetin flavonoid, which has high antioxidant activity in the DPPH free radical to calculate the IC_{50} of the extracts.

Determination of anti-AChE activity

AChE inhibition activity test was performed using the spectrophotometric method of Ellman et al. (1961), modified by Trevisan et al. (2003) for 96-well flat-bottomed microplates. For the preparation of the test plate, the following solutions were used per well: 25 µL of acetylthiocholine iodide (15 mmol L^{-1}), 125 µL of 5,5'-dithiobis- [2-nitrobenzoic] in the Tris/HCl

solution (50 mmol L^{-1}, pH = 8), with 0.1 mol L^{-1} NaCl and 0.02 mol L^{-1} $MgCl_2.6H_2O$. (3 mmol L^{-1}, DTNB), 50 µL of the Tris/HCl solution (50 mmol L^{-1}, pH = 8), with 0.1% of bovine serum albumin (BSA), 25 µL of the extract sample dissolved in ethanol (2 mg mL^{-1}) and diluted 10 times in the Tris/HCl solution (50 mmol L^{-1}, pH = 8) to obtain a final concentration of 0.2 mg. mL^{-1}. The absorbance was measured at 405 nm in the microplate reader (BIOTEK ELX 800, software Gen5 V2.04.11), for 30 seconds. Then, 25 µL of the enzyme acetylcholinesterase (0.25 $U.mL^{-1}$) was added and the absorbance was measured per minute until the total of 25 minutes of incubation of the enzyme. As a blanc control, the reactive mixture excluding the sample, and for the positive control, the alkaloid physostigmine was used. The values referring to the natural colorings of the extracts were extinguished from the analysis. The percentage of acetylcholinesterase inhibition was calculated by comparing the reaction rates (substrate hydrolysis) of the samples in relation to the blank (considered total AChE activity, 100%). The dilutions of the samples and the positive standard started from the mother solution with a concentration of 20 mg mL^{-1} and were: 200 µg mL^{-1}, 100 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12,5 µg mL^{-1}, 6,25 µg mL^{-1}, 3,12 µg mL^{-1}, 1,56 µg mL^{-1}, and 0,78 µg mL^{-1}. After normalizing the data, a non-linear regression curve test was performed using the Graph Pad Prism v5.01 statistical program to obtain the final results.

Statistical analysis

The statistical analysis was performed using the Graph Pad Prism v5.01 program, where the data were submitted to the one-way test of variance analysis (ANOVA) to determine the statistical differences followed by the multiple comparison between pairs by the Tukey test, considering significant values at $P < 0.05$. To analyze the correlation between the data, Pearson's correlation coefficient was used in the Microsoft Excel 2019 software, which measures the degree of linear correlation between two quantitative variables.

3. Results and Discussion

In the State's Cocó Park, 30 species of medicinal plants were collected and the plant part was chosen according to the popular use. About the families the most prevalent was Fabaceae (8), followed by Anacardiaceae (5), Rubiaceae (2) and Combretaceae (2). The activities of the plants are displayed in Table 2. The most common use of plants is for gastrointestinal diseases as diarrhea and dysentery (12/30), following the treatment of dermatitis, wounds (healing) and mycosis (9/30); for inflammation and infections - 7 plants; respiratory tract diseases such as bronchitis, asthma and cough - 6 plants; diabetes - 5 plants and for cancer or anti-tumor *Annona glabra*, *Cordia oncocalyx* and *Moringa oleifera*. An ethnobotanical survey with High School students about medicinal plants in Maranguape-Ceará showed that the most cited therapeutic indications were related to diseases of the respiratory, digestive and circulatory systems (Castro et al, 2021). In another study 22 plants from Caxias city of Maranhão State, cited by the population, being mainly indicated for poor digestion, insomnia, hypertension, cough, flu and inflammation (Silva et al, 2021). Then, these informations confirm that the medicinal plants present in Cocó Park are representatives of the popular use of plants for medicinal purposes. In general, these diseases can be related to oxidative stress and to the action of the acetylcholinesterase enzyme, then phenolic compounds can act in several pathogens and strengthen the immune system, contributing to treat Alzheimer´s disease.

Table 2. Species of medicinal plants present in Cocó State's Park, common name and popular medicinal indication.

Species (Family)	Common Name	Popular use	References
Anacardium occidentale L. (Anacardiaceae)	Cajueiro	Inflammation of the gums and throat, toothache, asthma, bronchitis, arthritis and diabetes.	Silva & Almeida, 2013.
Annona glabra L. (Annonaceae)	Araticum do Brejo	Chronic bronchitis, cancer, parasites and insects.	Cochrane et al., 2008.
Bauhinia forficata Link (Fabaceae)	Mororó	Diabetes, infections, processes inflammatory and pain.	López & Santos, 2015.
Brosimum gaudichaudii Trécul (Moraceae)	Inharé	Skin spots and dermatitis.	Agra et al., 2008.
Caesalpinia pulcherrima (L.) SW (Fabaceae)	Flamboyant Mirim	Infections, fevers, malaria, bronchitis, diarrhea and dysentery.	Kumbhare et al., 2012.
Cecropia pachystachya Trécul (Urticaceae)	Torém	Respiratory infections, diabetes and gonorrhea.	Souza et al., 2014.
Ceiba pentandra (L.) Gaertn. (Malvaceae)	Paineira	Bronchitis, asthma, cough, skin disease, dysentery, gonorrhea, eye diseases, arthritis and fever.	Loganayaki et al., 2013.
Cenostigma pyramidale (Tul.) E. Gagnon & G. P. Lewis (Fabaceae)	Catingueira	Inflammation, bronchitis, expectorant, depurative, intestinal infections and fever.	Silva et al., 2015.
Cordia oncocalyx Allemão (Boraginaceae)	Pau Branco do Sertão	Analgesic, antioxidant, anti-inflammatory and anti-tumor.	Guimarães et al., 2013.
Couroupita guianensis Aubl. (Lecythidaceae)	Abricó de Macaco	Stomach pains and skin diseases.	Kumar et al., 2011.
Crateva tapia L. (Capparaceae)	Trapiá	Respiratory tract infections, dysentery and fever.	Sharma et al., 2013.
Erythrina velutina Willdenow (Fabaceae)	Mulungu	Stress, insomnia, anxiety and depression.	Palumbo et al., 2016.
Genipa americana L. (Rubiaceae)	Jenipapo	Diabetes, fever and liver disease.	França, 2017.
Geoffroea spinosa Jacq. (Fabaceae)	Marizeira	Menstrual disorders and anemia.	Souza et al., 2015.
Guazuma ulmifolia Lam. (Sterculiceae)	Mutamba	Gastrointestinal and cardiovascular diseases.	Pereira et al., 2019.
Handroanthus impetiginosus (Mart. ex DC.) Mattos (Bignoniaceae)	Ipê Roxo	Diabetes, ulcers and syphilis.	Fonseca et al., 2017.
Hymenaea stigonocarpa Mart. ex Hayne (Fabaceae)	Jatobá do Cerrado	Anti-inflammatory, gastritis and ulcers.	Orsi et al., 2014.
Laguncularia racemosa (L.) C. F. Gaertn. (Combretaceae)	Mangue Branco	Fever and diarrhea.	Bandaranayake, 2002.
Libidibia ferrea (Mart. ex Tul.) L.P.Queiroz (Fabaceae)	Jucazeiro	Bacterial, healing and anti-inflammatory infections.	Kobayashi et al., 2015.
Mangifera indica L. (Anacardiaceae)	Mangueira	Constipation, cough, hiccup, bleeding, wounds, ulcers, hemorrhoids, dysentery and burns.	Parvez, 2016.
Mimosa tenuiflora (Mart.) Benth. (Fabaceae)	Jurema Preta	Burns, acne and skin problems.	Cruz et al., 2016.
Moringa oleífera Lam. (Moringaceae)	Moringa	Ulcer, inflammation, wounds, heart problem, cancer, stroke, obesity, anemia and liver damage.	Aja et al., 2014
Myracrodruon urundeuva M. Allemão) (Anacardiaceae)	Aroeira do Sertão	Diarrhea, dysentery and how to heal.	Freitas et al., 2018.
Spondias mombim L. (Anacardiaceae)	Cajazeira	Diarrhea, dysentery and herpes.	Silva et al., 2014.
Syzygium cumini (L.) Skeel (Myrtaceae)	Azeitona Preta	Diabetes mellitus	Cartaxo-Furtado et al., 2017.
Talisia esculenta (A. St.-Hil.) Radlk (Sapindaceae)	Pitombeira	Diarrhea, dehydration, low back pain and kidney problems.	Guarim Neto et al., 2003.
Tapirira guianensis Aublet (Anacardiaceae)	Pau Pombo	Leprosy, diarrhea and syphilis.	Rodrigues et al., 2017.
Terminalia catappa L. (Combretaceae)	Castanholeira	Gastritis, urinary tract infection, dermatitis, hepatitis, diarrhea and fever.	Silva et al., 2015.
Tocoyena formosa (Cham. & Schltdl.) (Rubiaceae)	Jenipapo Bravo	Cough, cystitis, torsion, rheumatism, kidney problems, cardiac, liver and cystitis.	Souza et al., 2013.
Ziziphus joazeiro Mart. (Rhamnaceae)	Juazeiro	Dermatitis, mycosis, dandruff, constipation, stomatitis, gastric ulcers, poor digestion and mouthwash.	Silva et al., 2011.

Source: Authors.

Cholinergic stimulation by administration of acetylcholinesterase inhibitors, enhances intestinal antimicrobial activity and prevents systemic dissemination of pathogenic bacteria, and the mechanism is a crucial pathway between neural and immune systems that acts at the mucosal interface to protect the host against invading pathogens (Al-Barazie et al., 2018).

Phenolic compounds including flavonoids are well-known antioxidants and presenting also many other important bioactivities for human health, curing and preventing many diseases, such as antibacterial, anti-cancer, cardioprotective, immunostimulant and anti-inflammatory and skin protective effect from UV radiation (Tungmunnithum et al., 2018).

The antioxidant and anticholinesterase activities of plant extracts may reveal the potential for the treatment of Alzheimer's Disease (AD). Bigueti, Lellis and Dias (2018) demonstrated that the intake of antioxidant substances contributed to the reduction of the disease incidence, and can be used as an alternative therapy for the treatment of the disease.

Previous studies (Achkar et al., 2014; Silva et al., 2010) have shown that the total phenol content above 100 µg mL^{-1} is already considered a high value in plant extracts, and in the ethanolic extracts of thirty plants from Cocó Park, 21 entered in this relation. Taking into account the best results in the present work, it is observed that ten species demonstrated antioxidant activity correlating linearly with the phenol content: *A. occidentale*, *C. pentandra*, *H. stigonocarpa*, *L. racemosa*, *L. férrea*, *M. indica*, *M. tenuiflora*, *M. urundeuva*, *S. mombim*, *T. cattapa,* whose total phenol content ranges from 297.46 ± 26.94 µg mL^{-1} (*S. mombim*) to 599.30 ± 17.08 µg mL^{-1} (*M. tenuiflora*) - with antioxidant activities with IC_{50} against DPPH radical ranging from 3.44 ± 0.16 to 3.73 ± 0.12 µg mL^{-1}, respectively (Table 3). Such a result is expected, since phenolic compounds have a high antioxidant capacity. Therefore, many medicinal plants present in Cocó Park are sources of antioxidant compounds.

Table 3. Content of Total Phenols (TP), Antioxidant Activity (DPPH) and Antiacetylcholinesterase (AChEI) of the ethanolic extracts of medicinal plants from Cocó's State Park.

Plants	**TP (mg GAE/g extract)**	**IC_{50} DPPH (μgmL^{-1})**	**AChEI (μgmL^{-1})**
Anacardium occidentale	$452.53^{c} \pm 15.15$	$4.04^{d} \pm 0,12$	$15.09^{l} \pm 0.04$
Annona glabra	$70.87^{o} \pm 15.97$	$163.61^{s} \pm 3,53$	$15.6^{m} \pm 0.15$
Bauhinia forficata	$229.22^{g} \pm 19.87$	$12.56^{i} \pm 0,33$	$29.2^{x} \pm 1.87$
Brosimum gaudichaudii	$146.11^{l} \pm 13.21$	$14.01^{j} \pm 0,96$	$23.97^{r} \pm 0.02$
Caesalpinia pulcherrima	$100.61^{n} \pm 14.46$	$17.58^{k} \pm 0,95$	$13.14^{h} \pm 0.01$
Cecropia pachistacia	$151.36^{l} \pm 3.03$	$11.84^{h} \pm 0,13$	$29.78^{x} \pm 0.08$
Ceiba pentandra	$352.58^{e} \pm 9.22$	$4.19^{d} \pm 0,16$	$15.87^{n} \pm 0.02$
Cenostigma piramidale	$414.70^{d} \pm 21.48$	$12.64^{i} \pm 0,11$	$7.04^{b} \pm 0.04$
Cordia oncocalyx	$71.73^{o} \pm 3.29$	$72.00^{o} \pm 0,59$	$26.55^{u} \pm 0.16$
Couroupita guianensis	$213.47^{h} \pm 6.61$	$24.20^{l} \pm 1,12$	$24.15^{s} \pm 0.07$
Crateva tapia	$114.61^{n} \pm 1.52$	$90.67^{p} \pm 1,36$	$12.04^{f} \pm 0.04$
Erythrina velutina	$134.73^{m} \pm 6.61$	$68.55^{o} \pm 4,64$	$23.20^{q} \pm 0.02$
Genipa americana	$33.25^{p} \pm 1.52$	$605.93^{u} \pm 40,70$	$27.81^{v} \pm 0.03$
Geoffroea spinosa	$188.10^{j} \pm 6.61$	$139.50^{r} \pm 2,58$	$28.10^{w} \pm 0.02$
Guazuma ulmifolia	$73.49^{o} \pm 5.25$	$89.00^{p} \pm 3,17$	$49.90^{y} \pm 0.09$
Handroanthus imperginosus	$74.37^{o} \pm 4.01$	$38.08^{n} \pm 1,74$	$12.63^{g} \pm 0.21$
Hymenaea stigonocarpa	$404.20^{d} \pm 10.50$	$5.82^{e} \pm 0,26$	$23.98^{r} \pm 0.11$
Laguncularia racemosa	$408.57^{d} \pm 14.46$	$6.32^{f} \pm 0.32$	$10.95^{c} \pm 0.02$
Libidibia ferrea	$394.58^{d} \pm 10.61$	$3.30^{c} \pm 0.18$	$29.15^{x} \pm 0.07$
Mangifera indica	$493.44^{b} \pm 13.89$	$7.29^{g} \pm 0.38$	$11.71^{d} \pm 0.02$
Mimosa tenuiflora	$599.30^{a} \pm 17.08$	$3.44^{c} \pm 0.16$	$29.34^{x} \pm 0.09$
Moringa oleifera	$97.11^{n} \pm 11.14$	$191.00^{t} \pm 3.08$	$20.76^{p} \pm 0.08$
Myracrodruon urundueva	$432.20^{c} \pm 5.46$	$3.09^{b} \pm 0.06$	$13.35^{i} \pm 0.00$
Spondias mombim	$297.46^{f} \pm 26.94$	$3.73^{d} \pm 0.12$	$28.10^{w} \pm 0.02$
Syzygium cumini	$178.48^{k} \pm 5.25$	$11.92^{h} \pm 0.23$	$14.10^{j} \pm 0.16$
Talisia esculenta	$71.74^{o} \pm 3.03$	$14.94^{j} \pm 0.44$	$12.60^{g} \pm 0.11$
Tapirira guianensis	$200.35^{i} \pm 21.21$	$13.20^{j} \pm 0.69$	$14.32^{k} \pm 0.05$
Terminalia catappa	$447.07^{c} \pm 21.85$	$6.09^{f} \pm 0.12$	$11.82^{e} \pm 0.12$
Tocoyena formosa	$140.86^{l} \pm 9.94$	$29.73^{m} \pm 1.42$	$24.18^{t} \pm 0.03$
Ziziphus joazeiro	$189.85^{j} \pm 10.93$	$123.04^{q} \pm 1.23$	$17.15^{o} \pm 0.19$
Physostigmine	-	-	$1.15^{a} \pm 0.05$
Quercetin	-	$1.32^{a} \pm 0.05$	-

All tests were performed in triplicate and the results were expressed as mean ± standard deviation; [1] milligram Equivalent to Gallic Acid per gram of extract; [2] Effective concentration to inhibit 50% of the free radical DPPH (2,2 – diphenyl – 1 – picryl – hydrazil); [3] Inhibitory concentration for 50% of acetylcholinesterase activity. (-) Tests not performed. Source: Authors.

The results obtained in the inhibition of AChE activity were compared to that of the alkaloid physostigmine, which was the first discovered natural inhibitor. Santos et al. (2018), determined the anticholinesterase activity of extracts and fractions from 54 plants and classified the action according to the IC_{50} values as: high potency (IC_{50} <20 μg mL^{-1}); moderate power (20 <IC_{50} <200 μg mL^{-1}) and low power (200 <IC_{50} <1000 μg mL^{-1}). Evaluating the results obtained in the AChE inhibition test, it is observed that 15 plants presented results below 20 μg mL^{-1}, therefore with a high inhibition power, they are: *A. occidentale*,

A. glabra, C. pulcherrima, C. pentandra, C. pyramidale, C. tapia, H. impetiginosus, L. racemosa, M. indica, M. urundeuva, S. cumini, T. esculenta, T. guianensis, T. catappa and Z. joazeiro.

In the correlation of the total phenol content with AChE enzyme inhibiting action, considering the 15 best results, but only six species that presented IC_{50} between 11 and 14 μg mL^{-1} correlate linearly with the levels of phenols: *C. pulcherrima*, *M. indica, M. urundeuva*, *S. cumini, T. guianensis* and *T. catappa*.

A weak correlation was obtained between the total phenolic content and AChE inhibition activity and these results are corroborated by studies by Barbosa Filho et al. (2006), who showed many other types of compounds exerting this activity. They report that out of 260 chemical compounds studied with AChE inhibiting action, only 51 were phenolic compounds (18 coumarins, 14 flavonoids, 13 benzenoids, 3 stilbenes, 2 lignans and 1 quinoid), however alkaloids were the majority class with 139 compounds. Another study reported by Santos et al. (2018) on the anti-acetylcholinesterase activity of plant species extracts, it was concluded that out of 54 plant species belonging to 29 different families, 36 compounds were identified, of which 16 showed potent inhibition, being superior to galantamine (1 terpene, 2 coumarins and 13 alkaloids) and another 20 compounds with lower potency (phenolic and flavonoid acids). Observing that the phenolic compounds did not show prominent AChE inhibition results, and the alkaloids represent the class with the highest potency in the evaluation.

Similarly, previous work with plants from living pharmacies, Morais et al. (2013) deduced that there was no linear correlation between AChE enzyme inhibition and the mean inhibition concentration of the DPPH radical - CE_{50} from the extracts of the tested plants.

Other studies have also shown that the mechanism of action of AChEIs is not limited to their effects on the neuron-to-neuron transmission involving acetylcholine but extends to their protective effects of a cell against free radical toxicity as well as increased production of antioxidants. A diet rich in polyphenols and polyunsaturated fatty acids helps boost the production of the brain's stem cells -neurogenesis- and strengthens their differentiation in different types of neuron cells. These results give support to the hypothesis that a diet made up of foods rich in antioxidant substances could delay the onset of DA or even slow down its evolution (Valente et al., 2009).

Thus, agents that combine antioxidant properties with the inhibition of AChE are expected to find usefulness in the management of AD (Tabet, 2006).

4. Conclusion

In conclusion, of the 30 species studied 6 stood out taking into account high levels of phenols and better antioxidant and acetylcholinesterase inhibition effects: *A. occidentale, C. pentandra, L. racemosa, M. indica, M. urundeuva, T. catappa*. Therefore, these plants can be considered the most promising as sources of phenolic compounds to be used in the treatment of Alzheimer's disease, due to their relevant action of inhibiting free radicals and the enzyme acetylcholinesterase.

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