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Neuroprotective activities of acai berries (*Euterpe* sp.): A review

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ABSTRACT

Dietary interventions rich in fruits and vegetables in aging people can reverse or mitigate age-related cognitive declines, delay the onset of neurodegenerative diseases (NDDs), and provide long-term health dividends. The novel food, popularly known as "Acai", is a berry belonging to the *Euterpe* genus of tropical palms trees and natively found in South America. *Euterpe oleracea* has been given much attention among scientists due to its high antioxidant capacity compared to other fruits and berries. Additionally, acai pulp composition analysis found that it contains various biologically active phytochemicals. In this review, we focused on current evidence relating to acai berry neuroprotection mechanisms and its efficacy in preventing or reversing neurodegeneration and age-related cognitive decline. A number of studies have illustrated the potential neuroprotective properties of acai berries. They have shown that their chemical extracts have antioxidant and anti-inflammatory properties and maintain proteins, calcium homeostasis, and mitochondrial function. Moreover, acai berry extract offers other neuromodulatory mechanisms, including anticonvulsant, antidepressant, and anti-aging properties. This neuromodulation gives valuable insights into the acai pulp and its considerable pharmacological potential on critical brain areas involved in memory and cognition. The isolated chemical matrix of acai berries could be a new substitute in research for NDD medicine development. However, due to the limited number of investigations, there is a need for further efforts to establish studies that enable progressing to clinical trials to consequently prove and ratify the therapeutic potential of this berry for several incurable NDDs.

Implication for health policy/practice/research/medical education:
This contribution is to construct a literature review that discusses the latest biological discoveries of acai berry extract as a neuroprotective agent that could be used as a pharmaceutical alternative for neurodegenerative diseases. This review will increase the interest in these berries as potential therapeutics for human brain diseases in the future.

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Introduction

Higher fruit and vegetable consumption is positively connected with lower neurodegenerative diseases (NDDs) risk (1-3). In these conditions, the neurons are gradually but irreversibly lost (4). Although neurogenesis occurs at a limited level in adult human brains (5), this is overwhelmed by progressive neural degradations leading to movement disabilities and a chronic decline in cognitive functions in NDD patients (6). Moreover, existing treatments for NDDs target a small area of the brain and are focused on symptomatic relief only, without modifying disease progression, thereby resulting in permanent disability or death of those afflicted (7). Therefore, finding agents that can target disease aetiologies may prevent or delay disease progression. However, collective evidence demonstrates that nutritional conditions, dietary habits, bioactive compounds derived from food, and exercise prevent the age-dependent decline in memory and cognition (8-10). Many dietary foods, phytochemicals, herbal secondary metabolites, and polyphenols have pharmacological benefits for human diseases (11-13). Colourful berries, especially those rich in polyphenols, have revealed an improvement in the motor, memory, and cognitive functions that are deteriorated with aging in animals, including humans (14-

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16). In agreement with this, investigations on the effects of anthocyanins and carotenoid-rich fruits showed promising outcomes in the prevention or retardation of NDDs (17-19). Data from a long-term cohort study of a 19.7-year follow-up of 2801 participants indicated that the risk of developing Alzheimer's disease and related dementias was reduced in individuals whose diet was high in flavonoids (20). Additionally, clinical trials demonstrated that regular consumption of fruits, such as grapes, berries, and oranges, had positive effects on cognitive function in patients with mild cognitive impairment as well as in old, healthy people (21,22). Therefore, there is a general consensus that high fruit intake can improve or prevent cognitive decline, thus resulting in a growing interest in this area of research. In this regard, the current research seeks to conduct a literature review on the use of acai berry extracts as a pharmaceutical option for the treatment and prevention of NDDs.

Acai berry origin and chemical composition

In the light of the evidence presented above about diets and their potentials in enhancing brain health, this review paper will focus on one novel food, popularly known as "Acai". It is a berry fruit of tropical palm trees belonging to the *Euterpe* genus, natively found in the Amazon region of South America and a few Caribbean islands (23). *Euterpe edulis*, *Euterpe precatoria*, and *Euterpe oleracea* are three species generating edible fruit, which were discovered in the Amazon region (23). The most consumed is *Euterpe oleracea* due to its high free radical scavenging capacity *in vitro,* which was discovered by Alexander Schauss in 1995 (24, 25). Since then, this novel berry received much attention among food scientists, being called a 'superfood' (23). *Euterpe oleracea* berry is a small round palm fruit, 1 to 2 cm in diameter, containing a single, dark coloured seed (25). A thin layer of edible purple pulp covers the seed (25). In the Para State of Brazil, acai palms are extensively distributed and cultivated (26), covering over 12 million hectares of flooded forest land near the Amazon River, and over 120 000 tons of the fruit is processed annually for its pulp (25). Acai berries are prepared before consumption by maceration in water to separate their seeds and obtain a thick, purple-coloured drink ('acai pulp') that is consumed as such or used in various types of drinks and food products (27). This viscous acai berry juice contains about 2.4% protein and 5.9% lipid (28).

In addition, nutritional composition studies on acai show the presence of dietary fibre, vitamin A, vitamin C, calcium, and iron (29). Commercialization of acai berry in its raw form is limited to the regional level in Brazil because it is naturally highly perishable (29). Consequently, national and international trading of acai berry usually occurs in a dry or frozen form (29). As a result of the highly rich bioactivate nutritional and phytochemical composition of acai berry, its pulp has been extensively examined (24,30). Acai berry pulp composition analysis found that it contains various biologically active phytochemicals and ample amounts of mono- and polyunsaturated fatty acids, which are not found in most fruits and other berries (31). Additionally, acai berry is a protein-rich fruit and has a high energy and nutritional value (Figure 1) (32). The phytochemicals found in acai pulp are anthocyanins, proanthocyanidins, and other flavonoids (24). Moreover, phytochemical analyses revealed that the acai berry has several types of anthocyanins, such as cyanidin, delphinidin, malvidin, pelargonidin, and peonidin; and has a great concentration of luteolin, quercetin, dihydrokaempferol, and chrysoerial (a unique flavone), as well as a number of other polyphenolics (30,33,34). According to Kang et al (35), the potential health effects of acai berry can be influenced by its flavonoid composition, such as orientin, homoorientin, vitexin, luteolin, chrysoerythol, quercetin, and dihydrokaempferol. A quantitative analysis of carotenoids in acai berry pulp detected five types of them: carotene, lycopene, astaxanthin, lutein, and zeaxanthin (36).

A considerable body of evidence has been gathered demonstrating that acai berry extract and its bioactive content exhibit many pharmacological activities such as anti-inflammatory, antioxidant, anticarcinogenic, and neuroprotective properties (33,35,37-39). Furthermore, several *in vivo* and *in vitro* toxicity evaluations of acai berry extract showed its safety and lack of genotoxic effects after its administration (38,40-45). On the other hand, an earlier study showed that high acai berry extract concentrations (5%, 10%, and 15% [wt/vol]) caused mutagenic effects when tested in eukaryotic *Saccharomyces cerevisiae* yeast cells; however, the mutagenic possibilities on human are little due to the fact that the acai berry extract concentrations used in that investigation were extremely elevated (46).

Several scientific review papers on acai berry extracts have been published (47-49), however, their aims focused on its antioxidant potential or general health benefits. Consequently, to our knowledge, there are currently no review reports concerning the neuroprotective activities of acai berries against many pathological mechanisms found in NDDs. Thus, the present contribution aims to develop a literature review discussing the recent biological findings of using acai berry as a pharmacological alternative for the treatment and prevention of NDDs.

Potential protecting roles of acai extracts in age-related NDDs have been examined. Many of these diseases are often multifactorial, arising from a combination of aging, genetic disorder, and exposure to one or more environmental factors, which directly or indirectly cause several cellular aetiologies; oxidative stress, chronic neuroinflammation, excitotoxicity, mitochondrial dysfunction, and irregular accumulation of protein in brain tissues (48, 53-56). Experiments demonstrated that acai berry extracts confer its neuroprotection by showing antioxidant and

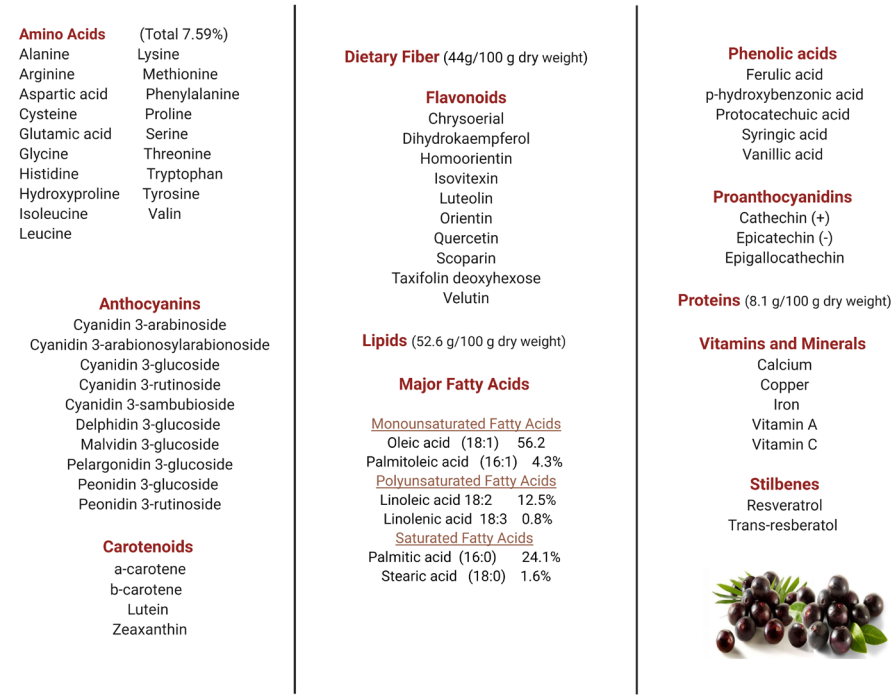

Figure 1. Phytochemicals and nutrient composition of the Amazonian acai berry identified to date (24,31-33,37,50-52).

anti-inflammatory activities, inhibiting toxic protein aggregation, and restoring calcium homeostasis and mitochondrial function (49). Additionally, acai berry exhibited antidepressive and anticonvulsant activities, which may be beneficial for people with such neuro-disorders (49). The neuromodulatory effects of acai berry diet supplementation on the vital brain areas that influence memory, cognition, and overall brain function will be discussed below.

Neuroprotective aspects of *Euterpe* sp. fruit

There is growing interest in acai fruits due to their broad usage in the food and cosmetics industries and their pharmaceutical potential. Acai berry parts such as pulp, leaves, roots, and seed oil were actually studied for pharmacological utilization, indicating specific biological activities based on their chemical composition. Potential health benefits of acai fruits are illustrated by many cell-based (Table 1), animal, and clinical studies (Table 2) (49). Although there are limited experiments investigating acai's impact on brain health or cognitive function, here we reviewed current results of acai berry protective actions on brain cells.

Antioxidant effects of acai berry

Oxidative damage is the common cytopathology of many NDDs. This damage is caused by an excessive accumulation of highly reactive free radicals associated with an impaired oxidant defence system, which is unable to adequately prevent this build-up of radicals (73,74). Free radicals, such as reactive oxygen (ROS), nitrogen (RNS) and chlorine (RCS) species, are defined as any atom or molecule that has one or more unpaired electrons (75). Oxidative damage can also be caused by some non-radicals, oxidizing agents, and/or agents that are easily transformed into radicals (76).

Typically, a low concentration of free radicals is essential for normal cellular function, on the other hand, they are harmful if found out of their regular place or present in abnormally high concentrations (75,77). Data indicates that neural cells undergo necrotic or apoptotic death when they fail to adequately respond to oxidative stress (76,78, 79). Cellular death by ROS occurs through the alteration of the essential biomolecules (lipid, protein, and nucleic acids) that can severely affect cell health and viability or induce a variety of cellular responses through the generation of secondary reactive species (76). The central nervous system (CNS) is more vulnerable to free radical damage than other organs due to the high level of oxygen intake by the brain, low levels of antioxidant enzymes, and abundance of highly oxidisable compounds, such as lipids, specifically the polyunsaturated fatty acids (80-83). Therefore, oxidative stress is one of the key mechanisms that contributes to neuronal degradation.

There is a clear explanation for the role of antioxidants in neutralizing the free radicals and protecting cells from their damage (84). Thus, finding substances rich in antioxidants can help protect neurons in the brain from oxidative damage. Acai berry polyphenolic-rich extract has effective and direct scavenging activities against most reactive oxygen species (29,36). Recently, many findings have shown that acai berry extract is capable of

Table 1. Recent findings of the neuroprotective roles of acai berry in *in vitro* models

Major observed effects after acai exposure	Level of Significance	Dose	Model	Reference
↓ NF-κB after velutin exposure in RAW-blue cells induced by LPS and OxLDL.	$P < 0.05$	Velutin acai extract; 5 μM, 2.5 μM, 1.25 μM, 0.625 μM used in LPS induced cells. Velutin acai extract; 10 μM, 5 μM and 2.5 μM on oxLDL induced cells.	*In vitro*. RAW-Blue mouse macrophage cell lines induced by LPS or oxLDL.	Kang et al (2011) (30)
↓ NO when compared with LPS treated microglia.	$P < 0.05$ in acai ethanol, ethyl acetate, and acetone fraction. $P < 0.001$ in methanol extract	The acai extract concentrations ranged from 50 to 1000 μg/mL for the methanol, ethyl acetate, and acetone fractions and from 10 to 250 μg/mL for the ethanol fraction.	*In vitro*. BV-2 murine microglial cells toxicity induced by LPS	Poulose et al (2012) (31)
↓ iNOS when compared with LPS treated microglia.	$P < 0.001$ in all acai fractions			
↓ TNF-α expression when compared with LPS alone.	$P = 0.009$ in ethyl acetate fraction, $P = 0.016$ for acetone fraction, $P < 0.001$ for methanol and ethanol fractions			
↓ p38-MAPK phosphorylation in LPS induced microglia.	$P < 0.001$			
↓ NF-κB phosphorylation except for the ethyl acetate fraction versus LPS alone.	$P < 0.001$			
↓ COX-2 expression in LPS induced microglia versus LPS alone.	$P < 0.001$			
↓ ROS by all acai genotypes in H_2O_2-treated cells.	$P < 0.05$	Hydroethanolic extracts from six acai (*Euterpe oleracea*) genotypes (L09P09, L22P13, BRS-PAMISTA, L11P09, L06P13 and L04P16) and an available commercial pulp at concentrations 0.5, 5.0 and 50 μg/mL.	*In vitro*. Human neuroblastoma cell line SH-SY5Y.	Torma et al (2017) (51)
↓ TNF-α and IL-6 production by velutin in LPS-treated RAW 264.7 and C57BL/6 macrophages.	$P < 0.05$	Velutin isolated from the pulp of acai at 2.5 to 20 μM (flavones as controls: luteolin, apigenin and chrysoeriol).	*In vitro*. RAW 264.7 peripheral macrophages and mouse C57BL/6 peritoneal macrophages with inflammation induced by LPS.	Xie et al (2012) (52)
↓ NF-κB activation by velutin in LPS-treated RAW 264.7 macrophages.	$P < 0.05$			
Inhibiting the degradation of NF-κB by velutin in LPS-treated RAW 264.7 macrophages.	ND			
Inhibiting p38-MAPK and JNK phosphorylation by velutin addition in LPS-treated RAW 264.7 macrophages.	ND			
↑ NDUFS7 and NDUFS8 expression.	Before $P < 0.001$ or after $P < 0.01$ rotenone exposure	Acai freeze-dried hydroalcoholic extract 5 μg/mL was added before and after rotenone.	*In vitro*. Human neuroblastoma cell line (SHSY5Y) toxicity induced via rotenone exposure.	Machado et al (2016) (57)
↓ ROS levels and lipid peroxidation in both experimental designs.	$P < 0.001$			

Table 1. Continued

Major observed effects after acai exposure	Level of Significance	Dose	Model	Reference
↓ Cellular proliferation vs LPS control.	$P < 0.05$	1 µg/mL of Freeze-dried hydroalcoholic acai extract.	*In vitro* BV-2 microglia cell line activated by LPS	de Souza et al (2020) (58)
↓ ROS generation vs LPS control.	$P < 0.05$			
↓ Pro-inflammatory cytokines vs LPS control.	$P < 0.05$			
↓ Caspase when compared to LPS control.	$P < 0.05$			
↓ Cellular proliferation in LPS-activated microglia to the negative control level (cells with normal media).	ND	0.001–1000 µg/mL of freeze-dried hydroalcoholic acai extract	*In vitro* Microglia EOC 13.31 cell line inflammatory induced by LPS or/ and nigericin	Cadoná et al (2021) (59)
↓ NO and ROS levels in LPS-activated microglia to the negative control level constituted of cells and normal media.	ND			
↓ NO levels after acai treatment of nigericin treated microglia like negative control.	ND			
↓NLRP3-infammasome induced in microglia via LPS as well as microglia induced by LPS and nigericin to negative control level.	ND			
↓ Caspase-1 and IL-1β expression levels in LPS and nigericin activated microglia to negative control.	ND			
↑ ATP levels similar to negative control, which were dropped by LPS and nigericin activation.	ND			
↓ Macrophage activation when compared with PHA-treated cells.	$P < 0.001$	Freeze-dried hydroalcoholic acai extract 0.001-1000 µg/mL.	*In vitro.* Macrophage cell line RAW 264.7 inflammation induced by PHA	Machado et al (2019) (60)
↓ ROS induced by PHA.	$P < 0.01$ at 100 µg/mL $P < 0.001$ at 0.001–10 µg/mL and 1000 µg/mL			
↓NO generated by PHA.	$P < 0.05$ at 1000 µg/mL, $P < 0.01$ at 0.001, 0.01, 0.1 and 500 µg/mL, and $P < 0.001$ at 0.005, 0.05, 1, 10, 100 µg/mL			
↓ Interferon-gamma (IFN-γ) when compared with PHA-treated cells.	$P < 0.01$			
↓ IL-1 β, IL-6, and ↓TNF-α when compared with PHA-treated cells.	$P < 0.001$			
↑ IL-10 which was reduced via PHA.	$P < 0.001$			
↓ NLRP3 inflammasome protein levels that were induced by PHA.	$P < 0.001$			
↓ Caspase 1,3,8 which were increased via PHA.	$P < 0.001$			
↓ Caspase 8 which were increased via PHA.	$P < 0.05$			
↓ NO production and iNOS expression that caused by LPS-exposure.	$P < 0.01$	2% of lyophilized acai pulps.	*In vitro*. BV-2 murine microglial cells were pretreated with 10% blood serum from rats fed acai then inflammation induced by LPS.	Carey et al (2017) (61)
↓ TNF-α in microglia activated by LPS exposure.	$P < 0.05$			

Table 1. Continued

Major observed effects after acai exposure	Level of Significance	Dose	Model	Reference
↓ NF-κB activity in LPS-induced DI TNC1 astrocytes.	$P < 0.001$	Hydroalcoholic acai extract 6.25, 12.5, 25, and 50 µg/mL.	*In vitro*. Rat astrocyte (DI TNC1) cell line stably transfected with the NF-κB or Nrf2-Antioxidant Response Element (ARE) constructs.	Ajit et al (2016) (62)
↑ ARE activity to 2-3 fold by acai alone.	$P < 0.001$			
↑ ARE activity in the presence of LPS to 10-fold by acai exposure.	$P < 0.001$			
↑ Antioxidant pathway Nrf2 expression, reaching 3-4 fold in untreated DI TNC1 astrocytes.	$P < 0.05$ at acai of 12.5 µg/mL, and $P < 0.001$ at 25 and 50 µg/mL			
↑ Antioxidant pathway HO-1 expression, reaching 3-4 fold in untreated DI TNC1 astrocytes.	$P < 0.05$ at 12.5 µg/mL acai, and $P < 0.01$ 25 and 50 µg/mL acai.			
↓ Toxicity of Ca^{2+} influx caused by dopamine application.	$P < 0.05$	1-5 µg/mL of aqueous extracts of freeze-dried acai pulp.	*In vitro*. Rodent Primary hippocampal neurons (HT22).	Poulose et al (2014) (63)
↓ The bafilomycin A1-induced build-up of autophagic vacuoles.	$P = 0.001$			
Reversed the reduction in the length of primary basal dendrites caused by wortmannin.	$P < 0.05$			
↑ Neuronal viability following $A\beta_{1-42}$ exposure.	$P < 0.01$ at 5 µg/mL, and $P < 0.05$ at 50 µg/mL	0.5, 5 and 50 µg/mL aqueous extract of freeze-dried acai pulp and skin powder.	*In vitro*. Rat PC12.	San Wong et al (2013) (64)
Fibril inhibition and alteration on $A\beta_{1-42}$ morphology.	$P < 0.05$			
↑ [^{3}H] TBOB binding to $GABA_A$ receptors in cortical neurons.	$P < 0.05$ at 5% acai and $P < 0.001$ at 25% acai	0–25% commercial clarified *Euterpe oleracea* Martius juice from Amazon Dreams (Belém, Pará, Brazil) in Hank's buffer (250 µL final volume).	*In vitro*. Primary cultures of neocortical neurons and cortical astrocytes	Arrifano et al (2018) (66)
↑ [^{3}H] flunitrazepam binding to $GABA_A$ receptors by acai at concentration 25% in cortical neurons.	$P < 0.01$			
↓ [^{3}H] GABA uptake in cortical neurons by acai at concentration 25%.	$P < 0.05$			
↓ [^{3}H] GABA uptake in astrocytes.	$P < 0.01$ at 10% and $P < 0.001$ at 25% acai.			

Abbreviations: $A\beta_{1-42}$, amyloid beta$_{1-42}$; ATP, adonise diphosphate; COX-2, cyclooxygenase-2; GABA, gamma-aminobutyric acid; H_2O_2 Hydrogen peroxide; HO-1, heme oxygenase-1; [3H] TBOB, [3H]-t-butylbicycloorthobenzoate; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; ND, not determined; NDUFS7, NADH: Ubiquinone Oxidoreductase Core Subunit S7; NDUFS8, NADH: Ubiquinone Oxidoreductase Core Subunit S8; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; OxLDL, oxidized low-density lipoprotein; p38-MAPK, p38 mitogen-activated protein kinase; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α' PHA, phytohemagglutinin.

Table 2. Acai berries neuroprotective effects in *in vivo* models

Major observed effects	Level of Significance	Dose and duration	Model	Reference
↑ Chemotaxis response in CL2355 strain.	$P < 0.001$ at 100 µg/mL acai	Fresh acai pulp was extracted using 80% methanol 50, 100, 200 µg/mL for 48 hours.	*In vivo.* *Caenorhabditis elegans* strain CL2355, which express $A\beta_{1-42}$ and impairs their chemosensory system. Transgenic worms (AM141) as Huntington's disease model which express polyQ *Caenorhabditis elegans* strain N2 (wild type)	Peixoto et al (2016) (29).
↓ PolyQ aggregation when compared with AM141 control worms.	$P < 0.01$ at 50 µg/mL and $P < 0.001$ at 100 and 200 µg/mL			
↓ Intracellular ROS accumulation in N2 worms.	$P < 0.001$			
↓ Protein oxidation levels in N2 worms.	$P < 0.05$ at 300 µg/mL			
Improved performance in the cognitive testing in aged rats.	$P < 0.05$	2% of lyophilized acai pulps for 8 weeks.	*In vivo* 19-month-old Fischer 344 rats.	Carey et al (2017) (61).
Protected against behavioural alterations caused by PTZ.	$P < 0.001$ and $P < 0.01$	10 µL/g /d of acai juice for 4 days.	*In vivo*. Male Swiss mice. Seizure model induced by pentylenetetrazol (PTZ)	Souza-Monteiro et al (2015) (65).
Prevented electrocortical changes induced by PTZ.	$P < 0.001$			
↓ Lipid peroxidation in the cerebral cortex that induced by PTZ.	$P < 0.05$			
The total energy intake, carbohydrate, protein, total lipids, and metabolic equivalent of task were unchanged after acai consumption.	ND	200 g/d of acai pulp for 4 weeks.	*In vivo* Thirty-five healthy women.	Barbosa et al (2016) (67).
↓ ROS level when compared with its level before acai intake.	$P = 0.004$			
↑ Total antioxidant capacity of polymorphonuclear cells (PMN) cells by 104% compared to before acai intake.	$P < 0.001$			
↑ CAT activity after acai intake when compared with the baseline results.	$P < 0.001$			
↓ Protein carbonyl after acai intake when compared with the baseline results.	$P = 0.027$			
↑ Sulfhydryl groups after acai when compared with the same groups at baseline.	$P < 0.001$			
↓ NADPH-oxidoreductase-2 (NOX2) in aged animals fed with acai-enriched diets.	$P < 0.05$, EO and EP	Freeze-dried acai powder = 2 % of the diet for 8 weeks. *Euterpe precatoria* (EP) and *Euterpe oleracea* (EO).	*In vivo*. 19-month-old male Fischer rats (aged rats).	Poulose et al (2017) (68).
↓ NF-κB in acai-consumed aged rats.	$P \leq 0.01$ EO, and EP			
↑ Glutathione S-transferase (GST) and SOD were observed in acai fed aged rats.	$P < 0.05$, EO and EP			
↑ Nrf2 transcription factor expression in acai fed rats.	$P < 0.05$, EO and EP			
Prevented CCl_4 inhibition of creatine kinase activity in rats.	$P < 0.01$ in cerebral cortex, and hippocampus, while $P < 0.001$ in cerebellum	Acai frozen pulp via oral gavage at a dose of 7 µL/g /d for 14 days.	*In vivo.* Male Wistar rat experimental model of hepatic encephalopathy provoked by CCl_4. The animals also presented neurological symptoms.	De Souza et al (2016) (69).
↓ Lipid peroxidation induced by CCl_4 in rat's cerebellum and cerebral cortex.	$P < 0.05$			
↓ Heightened carbonyl levels induced by CCl_4 in rats.	$P < 0.01$ in cerebellum, and $P < 0.001$ in cerebral cortex and hippocampus			
↑ CAT activity which was reduced in rat brain by CCl_4.	$P < 0.05$ in hippocampus and $P < 0.01$ in cerebellum			
↑ SOD activity which was reduced in CCl_4-treated rats.	$P < 0.05$ in cerebral cortex, and $P < 0.01$ in cerebellum and hippocampus			

Table 2. Continued

Major observed effects	Level of Significance	Dose and duration	Model	Reference
Improved neurobehavioral disturbance caused by MeHg when compared with MeHg only treated group.	$P < 0.05$	Clarified acai juice, 10 µL/g /d for 8 days.	*In vivo*. Male Swiss mice. Toxicity induced by MeHg.	Crespo-López et al (2019) (70).
↓ Lipid peroxidation which was elevated by MeHg.	$P < 0.05$			
↓ The elevated level of nitrite in MeHg treated animals to similar to those of	$P < 0.05$			
the control with when compared with MeHg only treated group. Prevented the reduction of TERT mRNA expression in the brain by MeHg.	$P < 0.001$			
Acai juice reduced the effects of mercury exposure while having no effect on mercury levels in the CNS.	ND			
Prevented the increase of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) caused by CCl_4 in the serum of rats.	$P < 0.05$	7 µL/g /d of acai juice for 14 days.	*In vivo*. Wistar rat model for hepatic encephalopathy induced by CCl_4. The animals used in these experiments presented neurological symptoms associated with hepatic encephalopathy.	de Souza et al (2015) (71).
↓ TNF-α, IL-1β and IL-18 levels in the cerebral cortex, hippocampus, and cerebellum which was induced by CCl_4.	$P < 0.05$			
Prevented the anhedonia-like state induced by LPS.	$P < 0.01$	10 µL/g /d body weight of acai juice for 4 days.	*In vivo*. Mouse model of depressive-like behavior induced by LPS.	Souza-Monteiro et al (2019) (72).
↑ Muscle activity which was completely inhibited by LPS.	$P < 0.05$			
Prevented immobility or the absence of response to stimulus caused by LPS.	$P < 0.001$			
↓ The lipid peroxidation which was generated by LPS exposure.	$P < 0.05$ in striatum and prefrontal cortex, and $P < 0.001$ in hippocampus			
↓ Nitrite levels that was induced in the hippocampus by LPS exposure.	$P < 0.01$			
↑ TERT mRNA expression, illustrating its anti-aging effect.	$P < 0.01$ in the hippocampus, and $P < 0.001$ in striatum and prefrontal cortex			
↑ TERT mRNA expression in all tested brain areas which was reduced by LPS treatment.	$P < 0.001$			

Abbreviations: $A\beta_{1-42}$, amyloid $beta_{1-42}$; CCl_4, carbon tetrachloride; COX-2, cyclooxygenase-2; IL-18, interleukin-18; IL-1β, interleukin 1 beta; LPS, lipopolysaccharide; MeHg, methylmercury; ND, not determined; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; polyQ, polyglutamine; ROS, reactive oxygen species; SOD, superoxide dismutase; TERT mRNA, telomerase reverse transcriptase; TNF-α, tumour necrosis factor-α.

regulating the antioxidant/pro-oxidant status (67,85-87). The chemical contents of acai berry, such as carotenoids, ascorbic acid, and phenolic compounds are responsible for their effective antioxidant actions (57,88).

Poulose et al. (68) showed that an acai berry rich diet could modulate oxidative stress and enhance endogenous antioxidant enzyme defence through decreased pro-oxidant NADPH-oxidoreductase-2 (NOX2) and increased expression of nuclear factor erythroid 2-related factor 2 (Nrf2) in the hippocampus and frontal cortex of elder rat brains. A study on a hepatic encephalopathy animal model with neurological symptoms illustrated that 14 days of acai berry treatment prevented creatine kinase (CK) activity inhibition, antioxidant enzyme catalase (CAT) activity reduction, oxidative damage involving increasing levels of lipid peroxidation and protein carbonyl groups in the cerebral cortex, hippocampus, and cerebellum (69). Moreover, the frozen pulp was able to restore the decrease in superoxide dismutase (SOD) activity in the hippocampus (69). A study investigating antioxidant activity of different acai berry genotypes and commercial pulp found that all hydroethanolic extracts had a potent scavenging property in reducing ROS produced by hydrogen peroxide (H_2O_2) in the human neuroblastoma SH-SY5Y cell line and no difference in the antioxidant activity was seen between different genotypes by ABTS and deoxyribose assays (51). Moreover, acai berry extract addition resulted in a significant reduction in ROS to the negative control levels in lipopolysaccharide (LPS)-activated microglia (58, 59). The behavioural analysis revealed that the consumption of commercial acai berry juice could improve neurobehavioral disturbance as a consequence of methylmercury (MeHg) as well as reduced lipid peroxidation and nitrite level induced by MeHg (70). In this study reduction of telomerase reverse transcriptase (TERT) mRNA expression in the brain as a consequence of mercury exposure was prevented by acai berry consumption. Thus, these studies give valuable evidence about the protection potential of acai berries against oxidative stress on brain cells, which could have a role in the treatment and/or prevention of NDDs.

Anti-inflammatory effects of acai

Deleterious conditions involving damage of the nervous system components by the immune response are known as neuroinflammatory disorders (53). This immune response in the brain can be triggered by infection, injury, trauma, genetic defect, or toxins causing resident immune cell (astrocytes and microglia) activation. This is followed by inflammatory signalling secretion (cytokines and chemokines) such as tumour necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin-6 (IL-6), leading to recruitment and infiltration of peripheral blood cells into the brain parenchyma (89).

One of the most evident pharmacological activities of acai berry, which has been recorded in many works of literature, is its anti-inflammatory effect. *In vitro* evaluation of acai berry on an inflammatory macrophage model induced via phytohemagglutinin demonstrated its anti-inflammatory potential through antioxidant pathway and modulation of nod-like receptor pyrin containing 3 (NLRP3) inflammasome proteins as well as a decrease of all pro-inflammatory cytokines and increase of anti-inflammatory cytokine interleukin-10 (IL-10) levels (60). Two percent acai berry administration to the diets of aging rats displayed a reduction of proinflammatory transcription factor nuclear factor κB (NF-κB) in the hippocampus (68). Carey et al (61) reported that aged rats fed with acai berry showed improved performance in cognitive testing compared with control rats. Blood serum from the same rats also had attenuated LPS-induced nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), nitric oxide (NO), and TNF-α production in BV-2 murine microglial cells. Acai berry exposed an inflammatory modulation by reducing TNF-α, IL-1 β, and IL-18 levels in the brains of rat models of hepatic encephalopathy that presented many neurological symptoms (71).

Moreover, Poulose et al (31) confirmed that acai berry extracts attenuated oxidative- and inflammatory-stress-induced signals on BV-2 microglial cells subjected to LPS through reduced NO release and decreased levels of inducible iNOS, COX-2, p38-mitogen-activated protein kinase (MAPK), TNF-α, and NF-κB. Similarly, acai berry extract was capable of reducing increased proinflammatory cytokines, IL-1β, IL-6, and TNF-α in LPS activated BV-2 microglial (58) Data from Kang et al (30) indicated that five flavonoids were isolated from acai berry pulp and only one of them, velutin, was able to inhibit the activation of inflammatory mediator factor NF-κB in RAW-blue cells induced by LPS. Investigating the modulatory effects of velutin isolated from acai berry on LPS-induced proinflammatory cytokines showed that it has the most potent inhibitory effects compared to other structurally similar flavones against NF-κB, mitogen-activated protein kinase p38, and JNK phosphorylation, consequently reducing the TNF-α and IL-6 production (52). A study exploring acai berry regulation of the oxidative/proinflammatory (NF-κB) and anti-oxidative (Nrf2) pathways in DI TNC1 astrocytes showed a reduction of LPS-induced NF-κB activity and induction of the anti-oxidation pathway through Nrf2 and HO-1 expression (62). Moreover, acai berry extract decreased cellular proliferation, IL-1β and restored NO in inflammatory activated microglia (59). Thus, it suggests the vital role of antioxidant-rich acai berry in the regulating and inhibition of the inflammatory response.

Calcium homeostasis

For several physiological conditions, calcium (Ca^{2+}) in neurons plays a significant role in controlling neuronal excitation, neurotransmitter release, gene expression, and eventually learning and memory (63). Excitotoxic

elevation of intraneuronal Ca^{2+} initiates lethal signalling cascades leading to necrotic cell death through free radical damage or/and activation of Ca^{2+} dependent catabolism enzymes (90). Moreover, this also triggers transcriptional activation of apoptotic programs (91, 92). Furthermore, Ca^{2+} can activate several vital enzymes that have the capability to destroy neurons, including protein kinase C, Ca^{2+}/calmodulin dependent protein kinase II, and nitric oxide synthase (93). Excessive Ca^{2+} build-up can also result in mitochondrial dysfunction (94,95). Neuronal Ca^{2+} dysregulation is linked with age-related neurodegenerative disorders (63). Thus, memory and cognitive functions can be maintained by correct Ca^{2+} homeostasis (63).

An *in vitro* study, acai berry pre-treatment protected rat primary hippocampal neurons from dopamine-induced Ca^{2+} dysregulation (63). Despite the need for further investigations to address the acai berry role in intraneuronal Ca^{2+} regulation, the results from previously conducted experiments suggest that quercetin and myricetin (other flavonoids) regulated intraneuronal Ca^{2+} concentration (96) and these bioflavonoids are richly found in acai berry pulp (63, 97). Since the majority of NDDs are associated with Ca^{2+} elevation, finding substances that can maintain and/or restore Ca^{2+} homeostasis gives promise to the prevention of these diseases.

Recovering of the mitochondrial function

Mitochondrial dysfunction has been implicated in neuronal death in all NDDs. Mitochondria are vital organelles in cells that perform crucial roles to maintain cellular function and viability (98,99). Mitochondrial damage leads to impaired energy generation, imbalanced calcium concentration, mitochondrial DNA (mtDNA) alteration, increased ROS, and release of pro-apoptotic factors, ultimately resulting in cell death via apoptosis or necrosis (98-100). Acai berry extract restored the impairment adonise diphosphate (ATP) levels in LPS, and nigericin inflammatory inducted microglia (59). In the same study, acai berry extract significantly lowered the pro-apoptotic caspase 1 level to control level (59). Increased levels of pro-apoptotic proteins, such as caspase 1, 3, and 8, were reduced in LPS exposed BV-2 microglia after acai berry extract treatment (58). An *in vitro* investigation pointed out that acai berry hydroalcoholic extract was able to reverse mitochondrial dysfunction induced by rotenone exposure in neuronal-like SH-SY5Y cells (57). In this study, functional recovery of the mitochondrial electron transport chain in neurons was mainly by overexpression of nuclear mitochondrial complex I subunit genes (NDUFS7 and NDUFS8) (57).

Protection from toxic protein accumulation

There is ample evidence that "proteotoxicity" is one of the consequences of neurodegeneration in NDDs (101, 102). Proteotoxicity is a condition affecting neuron viability, and it occurs when there is overproduction and/or impaired clearance of toxic protein in and around the brain tissue (101, 102). Neurons affected by toxic proteins undergo cell death due to impairment of the transcription process of specific genes, mitochondrial function, nucleocytoplasmic transport, and the protein/RNA quality control system (102-104). One of the main causes of protein aggregation is dysfunctional autophagy (105). In normal cellular autophagy, unwanted cytoplasmic substrates are degraded by lysosomes (105). Inhibition of autophagy causes protein alteration of the "quality control" mechanism leading to the accumulation of unwanted proteins and organelles in the brain, subsequently neuronal death (63). Therefore, protein homeostasis in the brain can be maintained by the autophagy mechanism.

Acai berry pre-treatment improved cell viability following exposure to human amyloid-β protein 1–42 ($A\beta_{1-42}$) (101). Moreover, in this study, acai berry extracts exhibited the most fibril inhibition and alteration of $A\beta_{1-42}$ morphology when compared with pure phenolics. Acai pre-treatment of neurons significantly reversed the basal dendrite length reduction and autophagy dysfunction induced by autophagy inhibitors such as bafilomycin A1 or wortmannin (63). Similarly, a diet supplemented with 2% of acai berry exhibited upregulation of autophagy markers in the hippocampus and frontal cortex of aging rat brains (68). In mutant strain *Caenorhabditis elegans* CL2355, which expressed $A\beta_{1-42}$ and have an impaired chemosensory system, pre-treatment with extract of acai berry enhanced the chemotaxis response and decreased both polyglutamine (polyQ) aggregation and protein oxidation levels (29). Collectively these studies reinforced that acai berry extracts exhibit protection against the excessive accumulation of misfolded cytotoxic proteins, which are pathological hallmarks of many NDDs. Thus, acai berry improves the protein homeostasis through molecular mechanisms and consequently leads to attenuation of neurotoxicity.

Anticonvulsant properties

It is reported that there is an association between the common neurodegenerative dementia syndromes and epileptic seizure phenomena, particularly in Alzheimer's disease (AD), Parkinson's disease dementia, prion diseases, and Huntington's disease (106). Epilepsy is a chronic neurological condition characterized by a predisposition to produce repeated epileptic seizures that are not triggered (107). Moreover, current anticonvulsant treatments do not suppress seizures in about 30% of patients (65). Thus, new treatment strategies based on bioactive compounds in diet or plants are practical options for avoiding, halting, or even reversing the seizures and epilepsy incidents (65).

Acai berry juice was able to protect against behavioural changes and reduce oxidative stress caused by seizures induced by pentylenetetrazol administration in mice (104). Hence, this study suggested that acai berry juice displayed anticonvulsant effects and additional neuroprotective

effects against lipid peroxidation connected with seizures. Similarly, acai berry treatment at 5%–25% concentration on primary cultures of cortical neurons and astrocytes showed its potential in the treatment of seizures and epilepsies by improving GABAergic neurotransmission (66). In this study, acai berry was able to interact with the $GABA_A$ receptor through increased agonist flunitrazepam binding and decreased antagonist t-butylbicycloorthobenzoate (TBOB) binding as well as inhibiting GABA reuptake, consequently leading to the accumulation of endogenous GABA in the synaptic cleft and enhanced inhibitory neurotransmission in the brain.

Antidepressant and anti-aging effects of acai

In most NDDs, patients develop depression symptoms in some stage of disease progression (108). This substantially leads to increased cognitive and motor symptom impairment, morbidity, stress on families, and the cost of illness (108). Since many synthetic anti-depression medications have various side effects, such as nausea, anxiety, drowsiness, insomnia, and sexual dysfunction, it is considered critical in finding a new antidepressant herb with fewer side effects (109). However, *in vivo* investigation by Souza-Monteiro et al. (72) on mouse models of depressive-like behaviour showed improvements in electromyographic measurements and prevention of the despair-like and anhedonia behaviours after acai berry treatment. In the same study, acai berry decreased the oxidative stress that developed in the depressive mouse model, thus protecting against hippocampal neuron loss. Moreover, this research highlighted that acai treatment caused an increase in telomerase reverse transcriptase (TERT mRNA) expression, illustrating its anti-aging and neuroprotective action.

Conclusion

Currently, considerable research attention has focused on acai berry due to its extraordinarily high antioxidant capacity. Some studies have illustrated the potential neuroprotective actions of acai. Many NDDs are the result of (1) oxidative stress, (2) chronic inflammation, (3) mitochondrial dysfunction, (4) calcium level elevation,

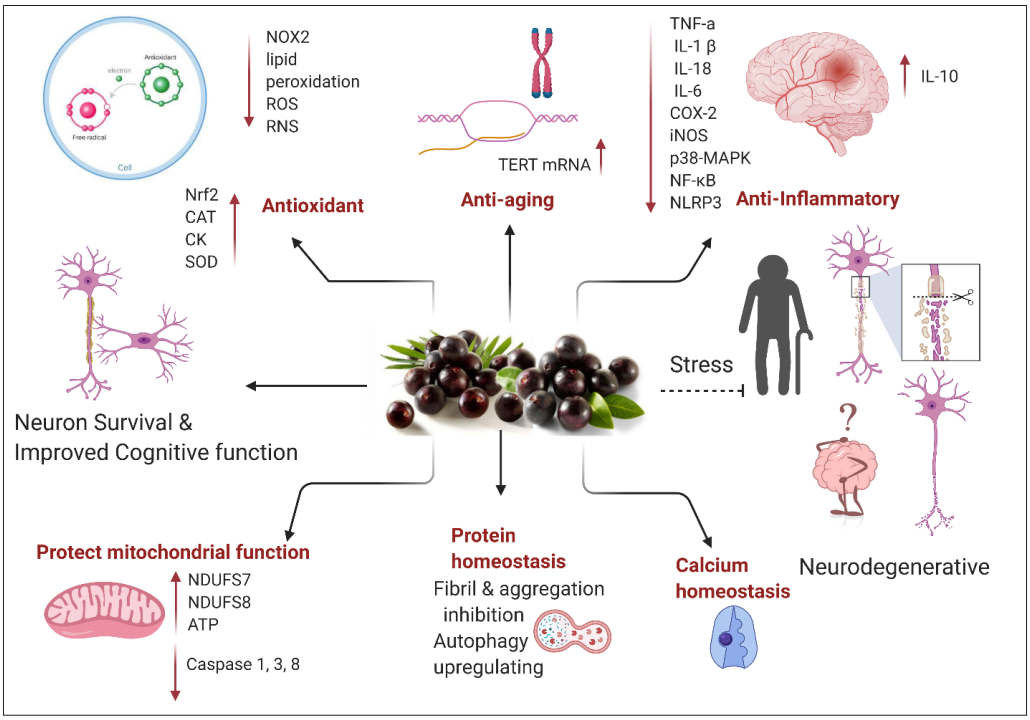

Figure 2. Known neuroprotective actions of *Euterpe* sp. fruits. Acai berry extracts are able to prevent neurodegenerative, maintain neurons' survival and cognitive function via the number of mechanisms summarized in this figure. First, the potential antioxidant action of acai berry extract involves decreasing oxidative stress markers such as NOX2, lipid peroxidation, ROS, and RNS, and increasing antioxidant defences system like Nrf2, CAT, CK, and SOD. Second, the anti-aging action resulted in an increase in the TERT mRNA. Third, the anti-inflammatory action of acai caused a reduction in inflammatory markers such as TNF-α, IL-1β, IL-18, IL-6, COX-2, iNOS, p38-MAPK, NF-κB, and NLRP3 while a rise in anti-inflammatory agent IL-10. Fourth, acai berry extracts are able to maintain the mitochondrial function via repairing the ATP production impairment and induce the expression of NDUFS7 and NDUFS8 while reducing the levels of the pro-apoptotic proteins, including caspases 1, 3, and 8. Fifth, acai berry extracts help to maintain the protein and calcium homeostasis in the neurons. Abbreviations: ATP, adonise diphosphate; CAT, catalase; CK, creatine kinase; COX-2, cyclooxygenase-2; IL-10, interleukin 10; IL-18, interleukin-18; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; NDUFS7, NADH: Ubiquinone Oxidoreductase Core Subunit S7; NDUFS8, NADH: Ubiquinone Oxidoreductase Core Subunit S8; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; NOX2, NADPH-oxidoreductase-2; Nrf2, nuclear factor erythroid 2-related factor 2; p38-MAPK, p38 mitogen-activated protein kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TERT mRNA, telomerase reverse transcriptase; TNF-α, tumour necrosis factor-α.

and (5) accumulation of misfolded or aggregate-proteins. Therefore, reducing the formation or improving the clearance of toxic bodies contributing to neurodegeneration may consequently prevent NDDs. Acai pulp fractions have shown promising beneficial effects and multi-target properties in regulating all five pathological processes, which have interdependent mechanisms (Figure 2). Moreover, acai berry extracts give hope in controlling other neurological disorders through other neuromodulatory properties such as anticonvulsant, antidepressant and anti-aging. This offers valuable insights into the acai berry pulp and its considerable pharmacological potential on brain cells. Although a number of bioactivate nutritional and phytochemical compositions in acai extracts have been identified, more research is being conducted to identify more biologically active components with therapeutic potential. The isolated chemical matrix of acai berry could be a new branch in research for NDDs medicine development.

Authors' contributions

Both authors invented the work's conception. MA designed studies collecting, literature interpretation, analysis and, article drafting. IM supervised the research and critical revision of the manuscript. Both authors read the article and agreed to the final version's publication.

Conflict of interests

Authors declare no conflict of interest.

Ethical considerations

Authors have carefully monitored ethical issues such as text plagiarism, duplicated publication, misconduct, data fabrication, and falsification.

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References

1. Carrillo J, Zafrilla MP, Marhuenda J. Cognitive function and consumption of fruit and vegetable polyphenols in a young population: is there a relationship? Foods. 2019;8(10):507. doi: 10.3390/foods8100507.
2. Grodzicki W, Dziendzikowska K. The role of selected bioactive compounds in the prevention of Alzheimer's disease. Antioxidants (Basel). 2020;9(3):229. doi: 10.3390/antiox9030229.
3. Jiang X, Huang J, Song D, Deng R, Wei J, Zhang Z. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. Front Aging Neurosci. 2017;9:18. doi: 10.3389/fnagi.2017.00018.
4. Obuobi S, Karatayev S, Chai CL, Ee PL, Mátyus P. The role of modulation of antioxidant enzyme systems in the treatment of neurodegenerative diseases. J Enzyme Inhib Med Chem. 2016;31(Suppl 3):194-204. doi: 10.1080/14756366.2016.1205047.
5. Bergmann O, Spalding KL, Frisén J. Adult neurogenesis in humans. Cold Spring Harb Perspect Biol. 2015;7(7):a018994. doi: 10.1101/cshperspect.a018994.
6. Batista P, Pereira A. Quality of life in patients with neurodegenerative diseases. J Neurol Neurosci. 2016;7(1):74 doi: 10.21767/2171-6625.100074.
7. Hussain R, Zubair H, Pursell S, Shahab M. Neurodegenerative diseases: regenerative mechanisms and novel therapeutic approaches. Brain Sci. 2018;8(9):177. doi: 10.3390/brainsci8090177.
8. Bigford GE, Del Rossi G. Supplemental substances derived from foods as adjunctive therapeutic agents for treatment of neurodegenerative diseases and disorders. Adv Nutr. 2014;5(4):394-403. doi: 10.3945/an.113.005264.
9. Macready AL, Kennedy OB, Ellis JA, Williams CM, Spencer JP, Butler LT. Flavonoids and cognitive function: a review of human randomized controlled trial studies and recommendations for future studies. Genes Nutr. 2009;4(4):227-42. doi: 10.1007/s12263-009-0135-4.
10. van de Rest O, Berendsen AA, Haveman-Nies A, de Groot LC. Dietary patterns, cognitive decline, and dementia: a systematic review. Adv Nutr. 2015;6(2):154-68. doi: 10.3945/an.114.007617.
11. Boese AD, Codorniu-Hernández E. Cross-talk between amino acid residues and flavonoid derivatives: insights into their chemical recognition. Phys Chem Chem Phys. 2012;14(45):15682-92. doi: 10.1039/c2cp42174g.
12. D'Archivio M, Filesi C, Varì R, Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. Int J Mol Sci. 2010;11(4):1321-42. doi: 10.3390/ijms11041321.
13. Rodriguez-Mateos A, Vauzour D, Krueger CG, Shanmuganayagam D, Reed J, Calani L, et al. Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. Arch Toxicol. 2014;88(10):1803-53. doi: 10.1007/s00204-014-1330-7.
14. Nilsson A, Salo I, Plaza M, Björck I. Effects of a mixed berry beverage on cognitive functions and cardiometabolic risk markers; a randomized cross-over study in healthy older adults. PLoS One. 2017;12(11):e0188173. doi: 10.1371/journal.pone.0188173.
15. Poulose SM, Carey AN, Shukitt-Hale B. Improving brain signaling in aging: could berries be the answer? Expert Rev Neurother. 2012;12(8):887-9. doi: 10.1586/ern.12.86.
16. Wink M. Modes of action of herbal medicines and plant secondary metabolites. Medicines (Basel). 2015;2(3):251-86. doi: 10.3390/medicines2030251.
17. Badshah H, Kim TH, Kim MO. Protective effects of anthocyanins against amyloid beta-induced neurotoxicity in vivo and in vitro. Neurochem Int. 2015;80:51-9. doi: 10.1016/j.neuint.2014.10.009.
18. Sun YX, Liu T, Dai XL, Zheng QS, Hui BD, Jiang ZF. Treatment with lutein provides neuroprotection in mice subjected to transient cerebral ischemia. J Asian Nat Prod Res. 2014;16(11):1084-93. doi: 10.1080/10286020.2014.939584.
19. Tarozzi A, Morroni F, Hrelia S, Angeloni C, Marchesi A, Cantelli-Forti G, et al. Neuroprotective effects of anthocyanins and their in vivo metabolites in SH-SY5Y cells. Neurosci Lett. 2007;424(1):36-40. doi: 10.1016/j.neulet.2007.07.017.
20. Shishtar E, Rogers GT, Blumberg JB, Au R, Jacques PF. Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring

Cohort. Am J Clin Nutr. 2020;112(2):343-53. doi: 10.1093/ajcn/nqaa079.
21. Kean RJ, Lamport DJ, Dodd GF, Freeman JE, Williams CM, Ellis JA, et al. Chronic consumption of flavanone-rich orange juice is associated with cognitive benefits: an 8-wk, randomized, double-blind, placebo-controlled trial in healthy older adults. Am J Clin Nutr. 2015;101(3):506-14. doi: 10.3945/ajcn.114.088518.
22. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br J Nutr. 2010;103(5):730-4. doi: 10.1017/s0007114509992364.
23. Schauss AG. Açaí (Euterpe oleracea Mart.): a macro and nutrient rich palm fruit from the Amazon rain forest with demonstrated bioactivities in vitro and in vivo. In: Watson RR, Preedy VR, eds. Bioactive Foods in Promoting Health. San Diego: Academic Press; 2010. p. 479-90. doi: 10.1016/b978-0-12-374628-3.00032-3.
24. Schauss AG, Wu X, Prior RL, Ou B, Huang D, Owens J, et al. Antioxidant capacity and other bioactivities of the freeze-dried Amazonian palm berry, *Euterpe oleraceae* Mart. (açaí). J Agric Food Chem. 2006;54(22):8604-10. doi: 10.1021/jf0609779.
25. Schauss AG. The effect of açaí (Euterpe spp.) fruit pulp on brain health and performance. In: Watson RR, Preedy VR, eds. Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease. San Diego: Academic Press; 2015. p. 179-86. doi: 10.1016/b978-0-12-411462-3.00019-9.
26. Gallori S, Bilia AR, Bergonzi MC, Barbosa WLR, Vincieri FF. Polyphenolic constituents of fruit pulp of *Euterpe oleracea* Mart. (açaí palm). Chromatographia. 2004;59(11):739-43. doi: 10.1365/s10337-004-0305-x.
27. Sabbe S, Verbeke W, Deliza R, Matta V, Van Damme P. Effect of a health claim and personal characteristics on consumer acceptance of fruit juices with different concentrations of açaí (*Euterpe oleracea* Mart.). Appetite. 2009;53(1):84-92. doi: 10.1016/j.appet.2009.05.014.
28. Del Pozo-Insfran D, Brenes CH, Talcott ST. Phytochemical composition and pigment stability of açaí (*Euterpe oleracea* Mart.). J Agric Food Chem. 2004;52(6):1539-45. doi: 10.1021/jf035189n.
29. Peixoto H, Roxo M, Krstin S, Wang X, Wink M. Anthocyanin-rich extract of açaí (Euterpe precatoria Mart.) mediates neuroprotective activities in Caenorhabditis elegans. J Funct Foods. 2016;26:385-93. doi: 10.1016/j.jff.2016.08.012.
30. Kang J, Xie C, Li Z, Nagarajan S, Schauss AG, Wu T, et al. Flavonoids from açaí (*Euterpe oleracea* Mart.) pulp and their antioxidant and anti-inflammatory activities. Food Chem. 2011;128(1):152-7. doi: 10.1016/j.foodchem.2011.03.011.
31. Poulose SM, Fisher DR, Larson J, Bielinski DF, Rimando AM, Carey AN, et al. Anthocyanin-rich açaí (*Euterpe oleracea* Mart.) fruit pulp fractions attenuate inflammatory stress signaling in mouse brain BV-2 microglial cells. J Agric Food Chem. 2012;60(4):1084-93. doi: 10.1021/jf203989k.
32. de Jesus ALT, Leite TS, Cristianini M. High isostatic pressure and thermal processing of açaí fruit (*Euterpe oleracea* Martius): effect on pulp color and inactivation of peroxidase and polyphenol oxidase. Food Res Int. 2018;105:853-62. doi: 10.1016/j.foodres.2017.12.013.
33. Pacheco-Palencia LA, Mertens-Talcott S, Talcott ST. Chemical composition, antioxidant properties, and thermal stability of a phytochemical enriched oil from açaí (*Euterpe oleracea* Mart.). J Agric Food Chem. 2008;56(12):4631-6. doi: 10.1021/jf800161u.
34. Schauss AG, Wu X, Prior RL, Ou B, Patel D, Huang D, et al. Phytochemical and nutrient composition of the freeze-dried Amazonian palm berry, *Euterpe oleraceae* Mart. (açaí). J Agric Food Chem. 2006;54(22):8598-603. doi: 10.1021/jf060976g.
35. Kang J, Li Z, Wu T, Jensen GS, Schauss AG, Wu X. Anti-oxidant capacities of flavonoid compounds isolated from açaí pulp (*Euterpe oleracea* Mart.). Food Chem. 2010;122(3):610-7. doi: 10.1016/j.foodchem.2010.03.020.
36. Kang J, Thakali KM, Xie C, Kondo M, Tong Y, Ou B, et al. Bioactivities of açaí (Euterpe precatoria Mart.) fruit pulp, superior antioxidant and anti-inflammatory properties to *Euterpe oleracea* Mart. Food Chem. 2012;133(3):671-7. doi: 10.1016/j.foodchem.2012.01.048.
37. Del Pozo-Insfran D, Percival SS, Talcott ST. Açaí (*Euterpe oleracea* Mart.) polyphenolics in their glycoside and aglycone forms induce apoptosis of HL-60 leukemia cells. J Agric Food Chem. 2006;54(4):1222-9. doi: 10.1021/jf052132n.
38. Schauss AG, Clewell A, Balogh L, Szakonyi IP, Financsek I, Horváth J, et al. Safety evaluation of an açai-fortified fruit and berry functional juice beverage (MonaVie Active®). Toxicology. 2010;278(1):46-54. doi: 10.1016/j.tox.2010.04.017.
39. Spada PD, Dani C, Bortolini GV, Funchal C, Henriques JA, Salvador M. Frozen fruit pulp of *Euterpe oleraceae* Mart. (açaí) prevents hydrogen peroxide-induced damage in the cerebral cortex, cerebellum, and hippocampus of rats. J Med Food. 2009;12(5):1084-8. doi: 10.1089/jmf.2008.0236.
40. Caiado RR, Peris CS, Lima-Filho AAS, Urushima JGP, Novais E, Badaró E, et al. Retinal toxicity of açaí fruit (Euterpe oleracea) dye concentrations in rabbits: basic principles of a new dye for chromovitrectomy in humans. Curr Eye Res. 2017;42(8):1185-93. doi: 10.1080/02713683.2017.1297995.
41. Choi YJ, Choi YJ, Kim N, Nam RH, Lee S, Lee HS, et al. Açaí berries inhibit colon tumorigenesis in azoxymethane/dextran sulfate sodium-treated mice. Gut Liver. 2017;11(2):243-52. doi: 10.5009/gnl16068.
42. Marques ES, Tsuboy MSF, Carvalho JCT, Rosa PCP, Perazzo FF, Gaivão IOM, et al. First cytotoxic, genotoxic, and antigenotoxic assessment of Euterpe oleracea fruit oil (açaí) in cultured human cells. Genet Mol Res. 2017;16(3). doi: 10.4238/gmr16039700.
43. Monge-Fuentes V, Muehlmann LA, Longo JP, Silva JR, Fascineli ML, de Souza P, et al. Photodynamic therapy mediated by açaí oil (Euterpe oleracea Martius) in nanoemulsion: a potential treatment for melanoma. J Photochem Photobiol B. 2017;166:301-10. doi: 10.1016/j.jphotobiol.2016.12.002.
44. Benatrehina PA, Pan L, Naman CB, Li J, Kinghorn AD. Usage, biological activity, and safety of selected botanical dietary supplements consumed in the United States. J Tradit Complement Med. 2018;8(2):267-77. doi: 10.1016/j.jtcme.2018.01.006.
45. Udani JK, Singh BB, Singh VJ, Barrett ML. Effects of açaí (Euterpe oleracea Mart.) berry preparation on metabolic parameters in a healthy overweight population: a pilot study. Nutr J. 2011;10:45. doi: 10.1186/1475-2891-10-45.
46. Spada PD, de Souza GG, Bortolini GV, Henriques JA,

Salvador M. Antioxidant, mutagenic, and antimutagenic activity of frozen fruits. J Med Food. 2008;11(1):144-51. doi: 10.1089/jmf.2007.598.
47. Chang SK, Alasalvar C, Shahidi F. Superfruits: phytochemicals, antioxidant efficacies, and health effects - a comprehensive review. Crit Rev Food Sci Nutr. 2019;59(10):1580-604. doi: 10.1080/10408398.2017.1422111.
48. de Oliveira NKS, Almeida MRS, Pontes FMM, Barcelos MP, de Paula da Silva CHT, Rosa JMC, et al. Antioxidant effect of flavonoids present in Euterpe oleracea Martius and neurodegenerative diseases: a literature review. Cent Nerv Syst Agents Med Chem. 2019;19(2):75-99. doi: 10.2174/1871524919666190502105855.
49. de Almeida Magalhães TSS, de Oliveira Macedo PC, Converti A, Neves de Lima Á A. The use of Euterpe oleracea Mart. as a new perspective for disease treatment and prevention. Biomolecules. 2020;10(6). doi: 10.3390/biom10060813.
50. Poulose S, Shukitt-Hale B. Functional role of walnuts and açaí fruits on brain health. Tropical and Subtropical Fruits: Flavors, Color, and Health Benefits. ACS Symposium Series. 1129: American Chemical Society; 2013. p. 171-187.
51. Torma PD, Brasil AV, Carvalho AV, Jablonski A, Rabelo TK, Moreira JC, et al. Hydroethanolic extracts from different genotypes of açaí (Euterpe oleracea) presented antioxidant potential and protected human neuron-like cells (SH-SY5Y). Food Chem. 2017;222:94-104. doi: 10.1016/j.foodchem.2016.12.006.
52. Xie C, Kang J, Li Z, Schauss AG, Badger TM, Nagarajan S, et al. The açaí flavonoid velutin is a potent anti-inflammatory agent: blockade of LPS-mediated TNF-α and IL-6 production through inhibiting NF-κB activation and MAPK pathway. J Nutr Biochem. 2012;23(9):1184-91. doi: 10.1016/j.jnutbio.2011.06.013.
53. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep. 2016;13(4):3391-6. doi: 10.3892/mmr.2016.4948.
54. Denzer I, Münch G, Friedland K. Modulation of mitochondrial dysfunction in neurodegenerative diseases via activation of nuclear factor erythroid-2-related factor 2 by food-derived compounds. Pharmacol Res. 2016;103:80-94. doi: 10.1016/j.phrs.2015.11.019.
55. Kovacs GG. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. Int J Mol Sci. 2016;17(2):189. doi: 10.3390/ijms17020189.
56. Lewerenz J, Maher P. Chronic glutamate toxicity in neurodegenerative diseases-what is the evidence? Front Neurosci. 2015;9:469. doi: 10.3389/fnins.2015.00469.
57. Machado AK, Andreazza AC, da Silva TM, Boligon AA, do Nascimento V, Scola G, et al. Neuroprotective effects of açaí (Euterpe oleracea Mart.) against rotenone in vitro exposure. Oxid Med Cell Longev. 2016;2016:8940850. doi: 10.1155/2016/8940850.
58. de Souza DV, Pappis L, Bandeira TT, Sangoi GG, Fontana T, Rissi VB, et al. Açaí (Euterpe oleracea Mart.) presents anti-neuroinflammatory capacity in LPS-activated microglia cells. Nutr Neurosci. 2020:1-12. doi: 10.1080/1028415x.2020.1842044.
59. Cadoná FC, de Souza DV, Fontana T, Bodenstein DF, Ramos AP, Sagrillo MR, et al. Açaí (Euterpe oleracea Mart.) as a potential anti-neuroinflammatory agent: NLRP3 priming and activating signal pathway modulation. Mol Neurobiol. 2021;58(9):4460-76. doi: 10.1007/s12035-021-02394-x.
60. Machado AK, Cadoná FC, Assmann CE, Andreazza AC, Duarte MMMF, dos Santos Branco C, et al. Açaí (Euterpe oleracea Mart.) has anti-inflammatory potential through NLRP3-inflammasome modulation. J Funct Foods. 2019;56:364-71. doi: 10.1016/j.jff.2019.03.034.
61. Carey AN, Miller MG, Fisher DR, Bielinski DF, Gilman CK, Poulose SM, et al. Dietary supplementation with the polyphenol-rich açaí pulps (Euterpe oleracea Mart. and Euterpe precatoria Mart.) improves cognition in aged rats and attenuates inflammatory signaling in BV-2 microglial cells. Nutr Neurosci. 2017;20(4):238-45. doi: 10.1080/1028415x.2015.1115213.
62. Ajit D, Simonyi A, Li R, Chen Z, Hannink M, Fritsche KL, et al. Phytochemicals and botanical extracts regulate NF-κB and Nrf2/ARE reporter activities in DI TNC1 astrocytes. Neurochem Int. 2016;97:49-56. doi: 10.1016/j.neuint.2016.05.004.
63. Poulose SM, Fisher DR, Bielinski DF, Gomes SM, Rimando AM, Schauss AG, et al. Restoration of stressor-induced calcium dysregulation and autophagy inhibition by polyphenol-rich açaí (Euterpe spp.) fruit pulp extracts in rodent brain cells in vitro. Nutrition. 2014;30(7-8):853-62. doi: 10.1016/j.nut.2013.11.011.
64. San Wong DY, Musgrave IF, Harvey BS, Smid SD. Açaí (*Euterpe oleraceae* Mart.) berry extract exerts neuroprotective effects against β-amyloid exposure in vitro. Neurosci Lett. 2013;556:221-6. doi: 10.1016/j.neulet.2013.10.027.
65. Souza-Monteiro JR, Hamoy M, Santana-Coelho D, Arrifano GP, Paraense RS, Costa-Malaquias A, et al. Anticonvulsant properties of Euterpe oleracea in mice. Neurochem Int. 2015;90:20-7. doi: 10.1016/j.neuint.2015.06.014.
66. Arrifano GPF, Lichtenstein MP, Souza-Monteiro JR, Farina M, Rogez H, Carvalho JCT, et al. Clarified açaí (Euterpe oleracea) juice as an anticonvulsant agent: in vitro mechanistic study of GABAergic targets. Oxid Med Cell Longev. 2018;2018:2678089. doi: 10.1155/2018/2678089.
67. Barbosa PO, Pala D, Silva CT, de Souza MO, do Amaral JF, Vieira RA, et al. Açaí (Euterpe oleracea Mart.) pulp dietary intake improves cellular antioxidant enzymes and biomarkers of serum in healthy women. Nutrition. 2016;32(6):674-80. doi: 10.1016/j.nut.2015.12.030.
68. Poulose SM, Bielinski DF, Carey A, Schauss AG, Shukitt-Hale B. Modulation of oxidative stress, inflammation, autophagy and expression of Nrf2 in hippocampus and frontal cortex of rats fed with açaí-enriched diets. Nutr Neurosci. 2017;20(5):305-15. doi: 10.1080/1028415x.2015.1125654.
69. de Souza Machado F, Kuo J, Wohlenberg MF, da Rocha Frusciante M, Freitas M, Oliveira AS, et al. Subchronic treatment with acai frozen pulp prevents the brain oxidative damage in rats with acute liver failure. Metab Brain Dis. 2016;31(6):1427-34. doi: 10.1007/s11011-016-9873-3.
70. Crespo-López ME, Soares ES, de Matos Macchi, Santos-Sacramento L, Takeda PY, Lopes-Araújo A, et al. Towards therapeutic alternatives for mercury neurotoxicity in the Amazon: unraveling the pre-clinical effects of the superfruit açaí (Euterpe oleracea Mart.) as juice for human consumption. Nutrients. 2019;11(11). doi: 10.3390/nu11112585.
71. de Souza Machado F, Marinho JP, Abujamra AL, Dani C, Quincozes-Santos A, Funchal C. Carbon tetrachloride increases the pro-inflammatory cytokines levels in different brain areas of Wistar rats: the protective effect of acai frozen

pulp. Neurochem Res. 2015;40(9):1976-83. doi: 10.1007/s11064-015-1693-z.
72. Souza-Monteiro JR, Arrifano GPF, Queiroz A, Mello BSF, Custódio CS, Macêdo DS, et al. Antidepressant and antiaging effects of açaí (Euterpe oleracea Mart.) in mice. Oxid Med Cell Longev. 2019;2019:3614960. doi: 10.1155/2019/3614960.
73. Markesbery WR, Carney JM. Oxidative alterations in Alzheimer's disease. Brain Pathol. 1999;9(1):133-46. doi: 10.1111/j.1750-3639.1999.tb00215.x.
74. Sayre LM, Smith MA, Perry G. Chemistry and biochemistry of oxidative stress in neurodegenerative disease. Curr Med Chem. 2001;8(7):721-38. doi: 10.2174/0929867013372922.
75. Florence TM. The role of free radicals in disease. Aust N Z J Ophthalmol. 1995;23(1):3-7. doi: 10.1111/j.1442-9071.1995.tb01638.x.
76. Halliwell B, Whiteman M. Measuring reactive species and oxidative damage in vivo and in cell culture: how should you do it and what do the results mean? Br J Pharmacol. 2004;142(2):231-55. doi: 10.1038/sj.bjp.0705776.
77. Schreck R, Baeuerle PA. A role for oxygen radicals as second messengers. Trends Cell Biol. 1991;1(2-3):39-42. doi: 10.1016/0962-8924(91)90072-h.
78. Perry G, Nunomura A, Lucassen P, Lassmann H, Smith MA. Apoptosis and Alzheimer's disease. Science. 1998;282:1268-9. doi: 10.1126/science.282.5392.1265h.
79. Perry G, Nunomura A, Smith MA. A suicide note from Alzheimer disease neurons? Nat Med. 1998;4(8):897-8. doi: 10.1038/nm0898-897.
80. Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. Physiol Rev. 1979;59(3):527-605. doi: 10.1152/physrev.1979.59.3.527.
81. Floyd RA, Carney JM. Free radical damage to protein and DNA: mechanisms involved and relevant observations on brain undergoing oxidative stress. Ann Neurol. 1992;32 Suppl:S22-7. doi: 10.1002/ana.410320706.
82. Shivasharan BD, Nagakannan P, Thippeswamy BS, Veerapur VP. Protective effect of Calendula officinalis L. flowers against monosodium glutamate induced oxidative stress and excitotoxic brain damage in rats. Indian J Clin Biochem. 2013;28:292-8. doi: 10.1007/s12291-012-0256-1.
83. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol. 2009;7(1):65-74. doi: 10.2174/157015909787602823.
84. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: a review. Eur J Med Chem. 2015;97:55-74. doi: 10.1016/j.ejmech.2015.04.040.
85. Peixoto H, Roxo M, Krstin S, Röhrig T, Richling E, Wink M. An anthocyanin-rich extract of açaí (Euterpe precatoria Mart.) increases stress resistance and retards aging-related markers in Caenorhabditis elegans. J Agric Food Chem. 2016;64(6):1283-90. doi: 10.1021/acs.jafc.5b05812.
86. de Lima Yamaguchi KK, Pereira LF, Lamarão CV, Lima ES, da Veiga-Junior VF. Amazon açaí: chemistry and biological activities: a review. Food Chem. 2015;179:137-51. doi: 10.1016/j.foodchem.2015.01.055.
87. de Liz S, Cardoso AL, Copetti CLK, de Fragas Hinnig, Vieira FGK, da Silva EL, et al. Açaí (Euterpe oleracea Mart.) and juçara (Euterpe edulis Mart.) juices improved HDL-c levels and antioxidant defense of healthy adults in a 4-week randomized cross-over study. Clin Nutr. 2020;39(12):3629-36. doi: 10.1016/j.clnu.2020.04.007.
88. Mathew S, Abraham TE, Zakaria ZA. Reactivity of phenolic compounds towards free radicals under in vitro conditions. J Food Sci Technol. 2015;52(9):5790-8. doi: 10.1007/s13197-014-1704-0.
89. Saavedra-López E, Casanova PV, Cribaro GP, Barcia C. Neuroinflammation in movement disorders. In: Steiner H, Tseng KY, eds. Handbook of Behavioral Neuroscience. Vol 24. Elsevier; 2016. p. 771-82. doi: 10.1016/b978-0-12-802206-1.00038-6.
90. Norenberg MD, Rao KV. The mitochondrial permeability transition in neurologic disease. Neurochem Int. 2007;50(7-8):983-97. doi: 10.1016/j.neuint.2007.02.008.
91. Londono C, Osorio C, Gama V, Alzate O. Mortalin, apoptosis, and neurodegeneration. Biomolecules. 2012;2(1):143-64. doi: 10.3390/biom2010143.
92. Pellegrini-Giampietro DE, Gorter JA, Bennett MV, Zukin RS. The GluR2 (GluR-B) hypothesis: Ca(2+)-permeable AMPA receptors in neurological disorders. Trends Neurosci. 1997;20(10):464-70. doi: 10.1016/s0166-2236(97)01100-4.
93. Tannenberg R, Dodd P. Cell damage/excitoxicity: excitotoxicity and neurodegenerative disease. In: Schwartzkroin PA, ed. Encyclopedia of Basic Epilepsy Research. Oxford: Academic Press; 2009. p. 114-9.
94. Atlante A, Calissano P, Bobba A, Giannattasio S, Marra E, Passarella S. Glutamate neurotoxicity, oxidative stress and mitochondria. FEBS Lett. 2001;497(1):1-5. doi: 10.1016/s0014-5793(01)02437-1.
95. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. J Physiol. 2000;529(Pt 1):57-68. doi: 10.1111/j.1469-7793.2000.00057.x.
96. Oyama Y, Fuchs PA, Katayama N, Noda K. Myricetin and quercetin, the flavonoid constituents of Ginkgo biloba extract, greatly reduce oxidative metabolism in both resting and Ca(2+)-loaded brain neurons. Brain Res. 1994;635(1-2):125-9. doi: 10.1016/0006-8993(94)91431-1.
97. de Moura C, dos Reis AS, da Silva LD, de Lima VA, Oldoni TL, Pereira C, et al. Optimization of phenolic compounds extraction with antioxidant activity from açaí, blueberry and goji berry using response surface methodology. Emir J Food Agric. 2018;30(3):180-9. doi: 10.9755/ejfa.2018.v30.i3.1639.
98. Krieger C, Duchen MR. Mitochondria, Ca(2+) and neurodegenerative disease. Eur J Pharmacol. 2002;447(2-3):177-88. doi: 10.1016/s0014-2999(02)01842-3.
99. Wu Y, Chen M, Jiang J. Mitochondrial dysfunction in neurodegenerative diseases and drug targets via apoptotic signaling. Mitochondrion. 2019;49:35-45. doi: 10.1016/j.mito.2019.07.003.
100. Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. Biochim Biophys Acta. 1998;1366(1-2):211-23. doi: 10.1016/s0005-2728(98)00114-5.
101. Douglas PM, Dillin A. Protein homeostasis and aging in neurodegeneration. J Cell Biol. 2010;190(5):719-29. doi: 10.1083/jcb.201005144.
102. Ruz C, Alcantud JL, Vives Montero F, Duran R, Bandres-Ciga S. Proteotoxicity and neurodegenerative diseases. Int J Mol Sci. 2020;21(16):5646. doi: 10.3390/ijms21165646.
103. Chung CG, Lee H, Lee SB. Mechanisms of protein toxicity in neurodegenerative diseases. Cell Mol Life Sci. 2018;75(17):3159-80. doi: 10.1007/s00018-018-2854-4.
104. Kim HJ, Taylor JP. Lost in transportation: nucleocytoplasmic transport defects in ALS and other neurodegenerative

diseases. Neuron. 2017;96(2):285-97. doi: 10.1016/j.neuron.2017.07.029.
105. Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell. 2011;146(5):682-95. doi: 10.1016/j.cell.2011.07.030.
106. Larner AJ. Epileptic seizures in neurodegenerative dementia syndromes. J Neurol Neurosci. 2010;1(1):1-3. doi: 10:3823/302.
107. Ono T, Galanopoulou AS. Epilepsy and epileptic syndrome. Adv Exp Med Biol. 2012;724:99-113. doi: 10.1007/978-1-4614-0653-2_8.
108. Baquero M, Martín N. Depressive symptoms in neurodegenerative diseases. World J Clin Cases. 2015;3(8):682-93.
109. Alamgeer M, Ahmad T, Hussain I, Mushtaq MN, Irshad N, Waseem M, et val. The use of plant extract in a mouse model of depression: a review. J Appl Pharm. 2013;5(4):159-63. doi: 10.21065/19204159.5.159.