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

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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 fruit, 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-
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 120000 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 polysaturated 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 chrysosorial (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, chrysoerythrol, 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...
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 neurodisorders (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 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
## Neuroprotective activities of acai berries

**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 | Poulouse et al (2012) (31) |
| ↓ iNOS when compared with LPS treated microglia. | $P = 0.009$ in ethyl acetate fraction, $P = 0.016$ for acetone fraction, $P < 0.001$ for methanol and ethanol fractions | | |
| ↓ TNF-α expression when compared with LPS alone. | $P < 0.001$ | Hydroethanolic extracts from six acai (*Euterpe oleracea*) genotypes (L09P09, L22P13, BRSPAMISTA, 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) |
| ↓ p38-MAPK phosphorylation in LPS induced microglia. | $P < 0.001$ | 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) |
| ↓ ROS by all acai genotypes in H$_2$O$_2$-treated cells. | $P < 0.001$ | | |
| ↓ 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. | $P < 0.001$ | | |
| ↓ 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 (SH-SY5Y) toxicity induced via rotenone exposure. | Machado et al (2016) (57) |
| ↓ ROS levels and lipid peroxidation in both experimental designs. | $P < 0.001$ | | |
Major observed effects after acai exposure

| Effect                                                                 | 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            | 1 μg/mL of freeze-dried hydroalcoholic acai extract.                  | *In vitro* Microglia EOC 13.31 cell line inflammatory induced by LPS or/ and nigericin |                                               |
| ↓ Pro-inflammatory cytokines vs LPS control.                           | *P* < 0.05            | 0.001–1000 μg/mL of freeze-dried hydroalcoholic acai extract         | *In vitro*                                                              | Cadoná et al (2021) (59)                     |
| ↓ Caspase when compared to LPS control.                                 | *P* < 0.05            | 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 |                                               |
| ↓ 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* BV-2 microglia cell line activated by LPS                  |                                               |
| ↓ NO and ROS levels in LPS-activated microglia to the negative control level constituted of cells and 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 |                                               |
| ↓ NO levels after aci treatment of nigericin treated microglia like negative control. | 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 |                                               |
| ↓ NLRP3-infammasome induced in microglia via LPS as well as microglia induced by LPS and nigericin to negative control level. | 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 |                                               |
| ↓ Caspase-1 and IL-1β expression levels in LPS and nigericin activated microglia to negative control. | 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 |                                               |
| ↑ ATP levels similar to negative control, which were dropped by LPS and nigericin activation. | 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 |                                               |
| ↓ 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, 0.001 at 0.001–10 μg/mL and 1000 μg/mL | Freeze-dried hydroalcoholic acai extract 0.001-1000 μg/mL.           | *In vitro* Macrophage cell line RAW 264.7 inflammation induced by PHA |                                               |
| ↓ NO generated by PHA.                                                 | *P* < 0.05            | 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)                     |
| ↓ Interferon-gamma (IFN-γ) when compared with PHA-treated cells.       | *P* < 0.01            | 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)                     |
| ↓ IL-1 β, IL-6, and ↓TNF-α 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)                     |
| ↑ IL-10 which was reduced via PHA.                                     | *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)                     |
| ↓ NLRP3 inflammasome protein levels that were induced by PHA.          | *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)                     |
| ↓ Caspase 1,3,8 which were increased via PHA.                          | *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)                     |
| ↓ Caspase 8 which were increased via PHA.                              | *P* < 0.05            | 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)                     |
| ↓ NO production and iNOS expression that caused by LPS-exposure.      | *P* < 0.01            | 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)                     |
| ↓ TNF-α in microglia activated by LPS exposure.                        | *P* < 0.05            | 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)                      |
| 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. | 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 | In vitro. | Rat astrocyte (DI TNC1) cell line stably transfected with the NF-κB or Nrf2-Antioxidant Response Element (ARE) constructs. |
| ↑ 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. | 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 Aβ$_{1-42}$ 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. | San Wong et al (2013) (64) |
| Fibril inhibition and alteration on Aβ$_{1-42}$ morphology. | $P < 0.05$ | | | |
| ↑ $[^3H]$ 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. | Arrifano et al (2018) (66) |
| ↑ $[^3H]$ flunitrazepam binding to GABA$\_A$ receptors by acai at concentration 25% in cortical neurons. | $P < 0.01$ | | | |
| ↓ $[^3H]$ GABA uptake in cortical neurons by acai at concentration 25%. | $P < 0.05$ | | | |
| ↓ $[^3H]$ GABA uptake in astrocytes. | $P < 0.01$ at 10% and $P < 0.001$ at 25% acai. | | | |

Abbreviations: Aβ$_{1-42}$, amyloid beta$_{1-42}$; ATP, adonise diphosphate; COX-2, cyclooxygenase-2; GABA, gamma-aminobutyric acid; H$_2$O$_2$, Hydrogen peroxide; HO-1, heme oxygenase-1; [3H]$^T$BOB, [3H]-t-butylibicycloorthobenzoate; 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 pulp | Fresh acai pulp was extracted using 80% methanol 50, 100, 200 μg/mL for 48 hours. | In vivo. | 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. | 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. | 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. | $P < 0.001$ | | | |
| 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. | 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. | In vivo. | Poulose et al (2017) (68). |
| ↓ NF-kB in acai-consumed aged rats. | $P < 0.01$ EO, and EP | Euterpe precatoria (EP) and Euterpe oleracea (EO). | | |
| ↑ Glutathione S-transferase (GST) and SOD were observed in acai fed aged rats. | $P < 0.05$, EO and EP | | | |
| ↑ NrT2 transcription factor expression in acai fed rats. | $P < 0.05$, EO and EP | | | |
| Prevented CCl4 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. | De Souza et al (2016) (69). |
| ↓ Lipid peroxidation induced by CCl4 in rat’s cerebellum and cerebral cortex. | $P < 0.05$ | | | |
| ↓ Heightened carbonyl levels induced by CCl4 in rats. | $P < 0.01$ in cerebral cortex and hippocampus | | | |
| ↑ CAT activity which was reduced in rat brain by CCl4. | $P < 0.05$ in hippocampus and $P < 0.01$ in cerebellum | | | |
| ↑ SOD activity which was reduced in CCl4-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 the control with when compared with MeHg only treated group. | *P* < 0.001          |                             |                              |                                               |
| Prevented the reduction of TERT mRNA expression in the brain by MeHg.                   | ND                    |                             |                              |                                               |
| Acai juice reduced the effects of mercury exposure while having no effect on mercury levels in the CNS. |                       |                             |                              |                                               |
| Prevented the increase of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) caused by CCl₄ 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 CCl₄. 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 CCl₄. | *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: Aβ₁₋₄₂, amyloid beta₁₋₄₂; CCl₄, carbon tetrachloride; COX-2, cyclooxygenase-2; IL-1β, interleukin-1β; 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; polQ, 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 (H₂O₂) 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 (Ca²⁺) in neurons plays a significant role in controlling neuronal excitation, neurotransmitter release, gene expression, and eventually learning and memory (63). Excitotoxic
elevation of intraneuronal $\text{Ca}^{2+}$ initiates lethal signalling cascades leading to necrotic cell death through free radical damage or/and activation of $\text{Ca}^{2+}$ dependent catabolism enzymes (90). Moreover, this also triggers transcriptional activation of apoptotic programs (91, 92). Furthermore, $\text{Ca}^{2+}$ can activate several vital enzymes that have the capability to destroy neurons, including protein kinase C, $\text{Ca}^{2+}/$calmodulin dependent protein kinase II, and nitric oxide synthase (93). Excessive $\text{Ca}^{2+}$ build-up can also result in mitochondrial dysfunction (94,95). Neuronal $\text{Ca}^{2+}$ dysregulation is linked with age-related neurodegenerative disorders (63). Thus, memory and cognitive functions can be maintained by correct $\text{Ca}^{2+}$ homeostasis (63).

An in vitro study, acai berry pre-treatment protected rat primary hippocampal neurons from dopamine-induced $\text{Ca}^{2+}$ dysregulation (63). Despite the need for further investigations to address the acai berry role in intraneuronal $\text{Ca}^{2+}$ regulation, the results from previously conducted experiments suggest that quercetin and myricetin (other flavonoids) regulated intraneuronal $\text{Ca}^{2+}$ concentration (96) and these bioflavonoids are richly found in acai berry pulp (63, 97). Since the majority of NDDs are associated with $\text{Ca}^{2+}$ elevation, finding substances that can maintain and/or restore $\text{Ca}^{2+}$ 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-$\beta$ protein 1–42 ($\text{A}1_{1-42}$) (101). Moreover, in this study, acai berry extracts exhibited the most fibril inhibition and alteration of $\text{A}1_{1-42}$ 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 $\text{A}1_{1-42}$ 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\(_\text{A}\) 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](image.png)

**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, adenosine 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 Oxidoreductase Core Subunit S7; NDUFS8, NADH 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 bioactive 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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