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Article

Neuroprotective potential of the Amazonian fruits *Euterpe oleracea* Mart. and *Paullinia cupana* Kunth

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Acai (Euterpe oleracea Mart.) and guarana (Paullinia cupana Kunth) are native species from the Amazon Forest that in folk medicine are used to treat several diseases due to their anti-inflammatory and antioxidant properties. This review brings together findings from different studies on the potential neuroprotective effects of acai and guarana, highlighting the importance of the conservation and sustainable exploitation of the Amazon Forest. A bibliographic survey in the PubMed database retrieved indexed articles written in English that focused on the effects of acai and guarana in *in vitro* and *in vivo* models of neurodegenerative diseases. In general, treatment with either acai or guarana decreased neuroinflammation, increased antioxidant responses, ameliorated depression, and protected cells from neurotoxicity mediated by aggregated proteins. The results from these studies suggest that flavonoids, anthocyanins, and carotenoids found in both acai and guarana have therapeutic potential not only for neurodegenerative diseases, but also for depressive disorders. In addition, acai and guarana show beneficial effects in slowing down the physiological aging process. However, toxicity and efficacy studies are still needed to guide the formulation of herbal medicines from acai and guarana.

Keywords: Acai. Anti-inflammatory. Antioxidant. Guarana. Neurodegenerative diseases.

INTRODUCTION

According to the World Health Organization (WHO), the elderly population (> 60 years old) will increase from 12% in 2015 to 22% in 2050 and projections indicate that in 2030 there will be 1.4 billion people aged 60 years and over. This increment in the populational age represents not only a social demographic problem but also a medical one (Rudnicka *et al*., 2020). Aging is one of the main risk factors for several neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases (AD, PD, and HD, respectively) (Kritsilis *et al*., 2018). AD affects approximately 55 million people worldwide and is more frequent between 75 and 84 years old (Alzheimer's Association, 2021; WHO, 2022), whereas PD is the second most prevalent neurodegenerative disease affecting 2-3% of the population over 65 years old (Poewe *et al*., 2017). Moreover, HD, which affects 5 to 7 individuals per 100,000 inhabitants aged between 30 and 50 years (Bruzelius *et al.,* 2019), is also an important neuropathology (Shawki *et al*., 2021). In a simplified way, AD, PD, and HD mainly impair neuronal structures and functions in part due to the aberrant accumulation of certain aggregated proteins: amyloid-beta (Aβ) in AD, α-synuclein in PD (Kulenkampff *et al*., 2021;Shawki *et al*., 2021), and huntingtin (HTT) in

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HD. It is also well accepted that oxidative damage and inflammation contribute to neuronal loss (Angelova, 2021; Subhramanyam *et al*., 2019). Concerted international efforts focus on discovering neuroprotective agents that can either slow down the progression or cure these diseases (Alzheimer's Association, 2021;Zhang *et al*., 2021).

Therapeutic plants have been used for millennia and beyond their use in traditional medicine by the Amazonian population (Tobouti *et al*., 2017), some native plants are also commercially used. For example, Copaiba (*Copaífera officinalis* L.) and Andiroba (*Carapa guianensis* Aubl.) are used as anti-inflammatory and antimicrobial herbal medicines for wound healing (Wanzeler *et al*., 2018). Here we review studies on the potential neuroprotective effects of two native species from the Amazon Forest, acai (*Euterpe oleracea* Mart.) and guarana (*Paullinia cupana* Kunth), in in vitro and in vivo models of neurodegenerative diseases.

BOTANICAL DESCRIPTION, DISTRIBUTION, AND TRADITIONAL USES

Euterpe oleracea Mart. belongs to the *Arecaceae* family of the *Arecales* order and is a large palm tree popularly known as acai-do-para, acai, assai, or huasai, which means "fruit that cries". It is native to tropical South America, being found mostly in the Amazon River basin, predominantly in the Eastern Amazon that includes the states of Para, Amapa, Tocantins, and Maranhao (de Oliveira, Schwartz, 2018; Matos *et al*., 2017; Ulbricht *et al*., 2012). *Euterpe oleracea* is a multistem palm with up to 25 stems per clamp;its trunk reaches 30 m high with a maximum diameter of 18 cm. Each stem holds an arrangement of 10-12 compound leaves of 3.5 m in length that are pinned in a spiral, and the inflorescence is below the leaf, to protect it from the sun. The acai has two varieties: a small dark black-purple rounded fruit, and other with a green epicarp, known as white acai (Dall' Acqua *et al*., 2015; de Oliveira, Schwartz, 2018; Pompeu, Silva, Rogez, 2009). Nowadays, acai is very important for the economy of the Amazon region, especially in the state of Para (de Oliveira, Schwartz, 2018). The acai juice is obtained by macerating the fruit with water that is then sold unprocessed and pasteurized or as mixed frozen pulp, being consumed worldwide as fruit mixes and ice creams. In the Amazon region, it is consumed mainly as a dish with manioc flour or tapioca flour and served with fish or shrimp (de Oliveira *et al*., 2019; Pompeu, Silva, Rogez, 2009).

In folk medicine, especially in the poorest regions of Brazil, acai is used to relieve pain and flu symptoms, and also topically to treat acne (Matheus *et al*., 2006). The dark green oil obtained from the fruit is used as an anti-diarrheal (da Silva *et al*., 2021; Plotkin, Balick, 1984), whereas root infusion is used for jaundice and root decoction is used for malaria, diabetes, liver disorders, hair loss, hemorrhage, kidney diseases, as well as menstrual and muscle pain (Ulbricht *et al*., 2012). In addition, the grated fruit rind is used topically for skin ulcers and fruit seeds prepared as a liquid extract by infusion are used to treat fever (Heinrich, Dhanji, Casselman, 2011).

Paullinia cupana Kunth belongs to the family *Sapindales* of the order *Sapindaceae* and is native to Guyana, Venezuela, Ecuador, Peru, and Brazil, where it is mainly cultivated in the states of Amazonas, Para, Acre, Mato Grosso, and Bahia (Marques *et al*., 2019). *Paullinia cupana* is an evergreen climbing shrub with branches measuring 4-8 mm in diameter, leaves measure 40 cm in length and the inflorescence may be longer than 30 cm (Marques *et al*., 2019). The fruit known as guarana, guarana-da-Amazonia, guaranaina, or uarana is a capsule that goes from yellowish orange to red and contains dark seeds that are covered partially by a white aril (Marques *et al*., 2019; Schimpl *et al*., 2013).

Some properties of guarana were described in the late 17th century, such as the antipyretic, analgesic, anti-spasmodic, and diuretic effects (Henman, 1982). In folk medicine the whole guarana fruit prepared as a juice is sold as a fortifier, stimulant, tonic, antidote to fever, to fight mental and physical exhaustion, a preventive medicine against hardening of the arteries and to treat migraines (Smith, Atroch, 2010). There are also claims that drinking guarana juice in the morning before breakfast could render aphrodisiac effects and protect from malaria and amoebic dysentery (Henman, 1982). The native population used to chew guarana seeds

or dissolve the powder in food or drinks (Kuri, 2011). Nowadays, it is commercialized by the energy and soft drink industry, and also by the pharmaceutical and cosmetic industries (Henman, 1982; Marques *et al*., 2019).

In addition to these traditional uses, *Euterpe oleracea* Mart. and *Paullinia cupana* Kunth are widely studied as functional foods, mainly due to their chemical constituents that present anti-inflammatory and antioxidant potential (Dalonso, Petkowicz, 2012; Yamaguti-Sasaki *et al*., 2007).

CHEMICAL COMPOSITION

Euterpe oleracea Mart. fruit is rich in bioactive compounds with high protein, fiber, and mineral content, being composed mostly of phenolic compounds (Pacheco-Palencia, Duncan, Talcott, 2009; Torma *et al*., 2017). The anthocyanins belong to the flavonoid class and are present in high amounts in acai, predominantly cyanidin 3-glucoside (0.5 $mg \cdot g^{-1}$) and cyanidin 3-rutinoside (0.6 $mg \cdot g^{-1}$), which are responsible for its purple colour (de Oliveira, Schwartz, 2018; Pacheco-Palencia, Duncan, Talcott, 2009; da Silveira *et al*., 2019). Among non-anthocyanins flavonoids, acai has a greater presence of luteolin (0.9 mg/100 g), rutin (3.4 mg/100 g), orientin (20.9 $mg \cdot g^{-1}$), and isoorientin (40.2 $mg \cdot g^{-1}$) (Garzón *et al*., 2017; da Silveira *et al*., 2019). As phenolic acids, there are vanillic acid (40.0 $mg \cdot g^{-1}$), syringic acid (19.0 $mg \cdot g^{-1}$), and caffeic acid (9.0 $mg \cdot g^{-1}$) (da Silveira *et al*., 2019). The major carotenoids are β-carotene (27.3 μg/g) and lutein (9.5 μg/g), and the main vitamins are vitamin A (retinol) (1002 IU/100 g) and vitamin E (α-tocopherol) (321.9 $mg \cdot g^{-1}$) (Lucas, Zambiazi, Costa, 2018; Schauss *et al*., 2006; da Silveira *et al.,* 2019) (Figure 1).

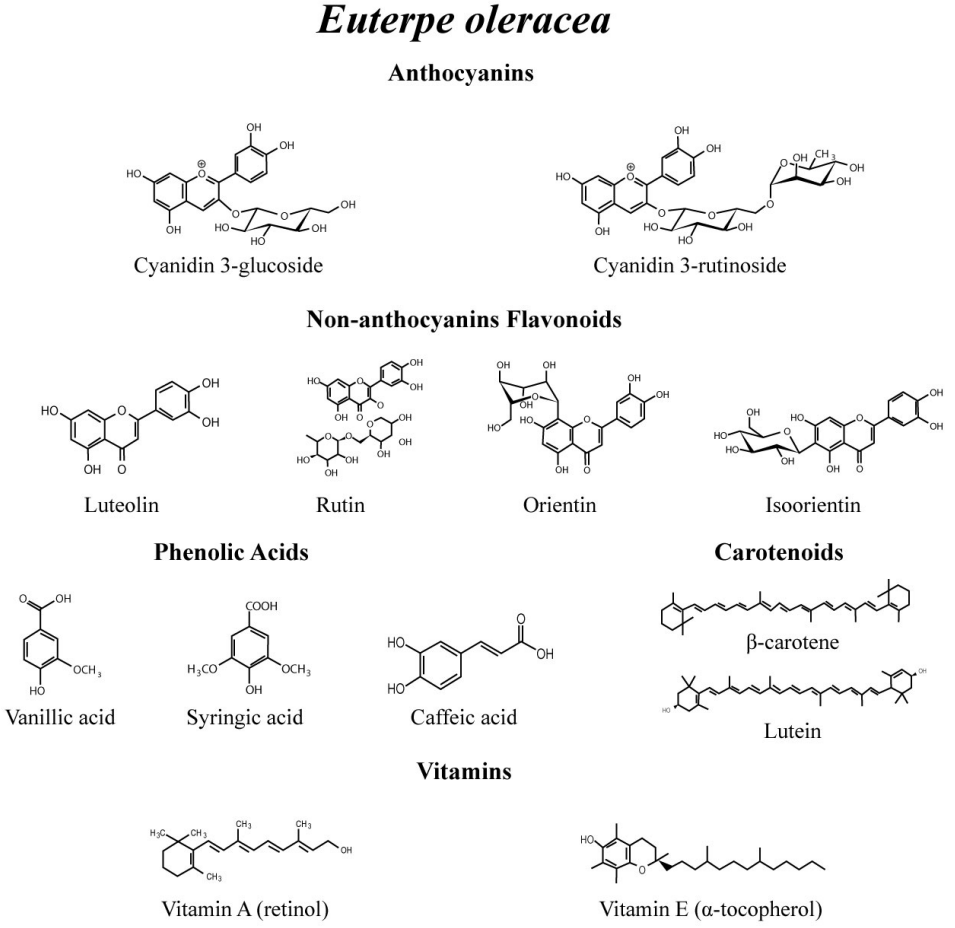

FIGURE 1 - Bioactive compounds from *Euterpe oleracea*.

Paullinia cupana Kunth seeds have high amounts of methylxanthines, flavan-3-ols, and proanthocyanidins and, in smaller quantities, contain saponins, starch, polysaccharides, and fats (Dalonso, Petkowicz, 2012; Henman, 1982;Yamaguti-Sasaki *et al*., 2007). The major methylxanthine is caffeine (2-8%;39.8 g/100 g) (Yonekura *et al*., 2016) that accounts for the energetic and stimulating properties (Higgins, Tuttle, Higgins, 2010) and is found in concentrations 2.7-5.8% higher than in coffee seeds (Pagliarussi, Freitas, Bastos, 2002). The other methylxanthines found are theobromine (0.4 g/100 g) and theophylline (1.8 g/100 g) (Santana, Macedo, 2018; Schimpl *et al*., 2013). As flavan-3-ols, there are catechin (30 mg/g) and epicatechin (20 mg/g) (Mendes *et al*., 2019), as well as procyanidin B1 (3.7 mg/g) and procyanidin B2 (3.4 mg/g) that are found in the seeds (Mendes *et al*., 2019) (Figure 2).

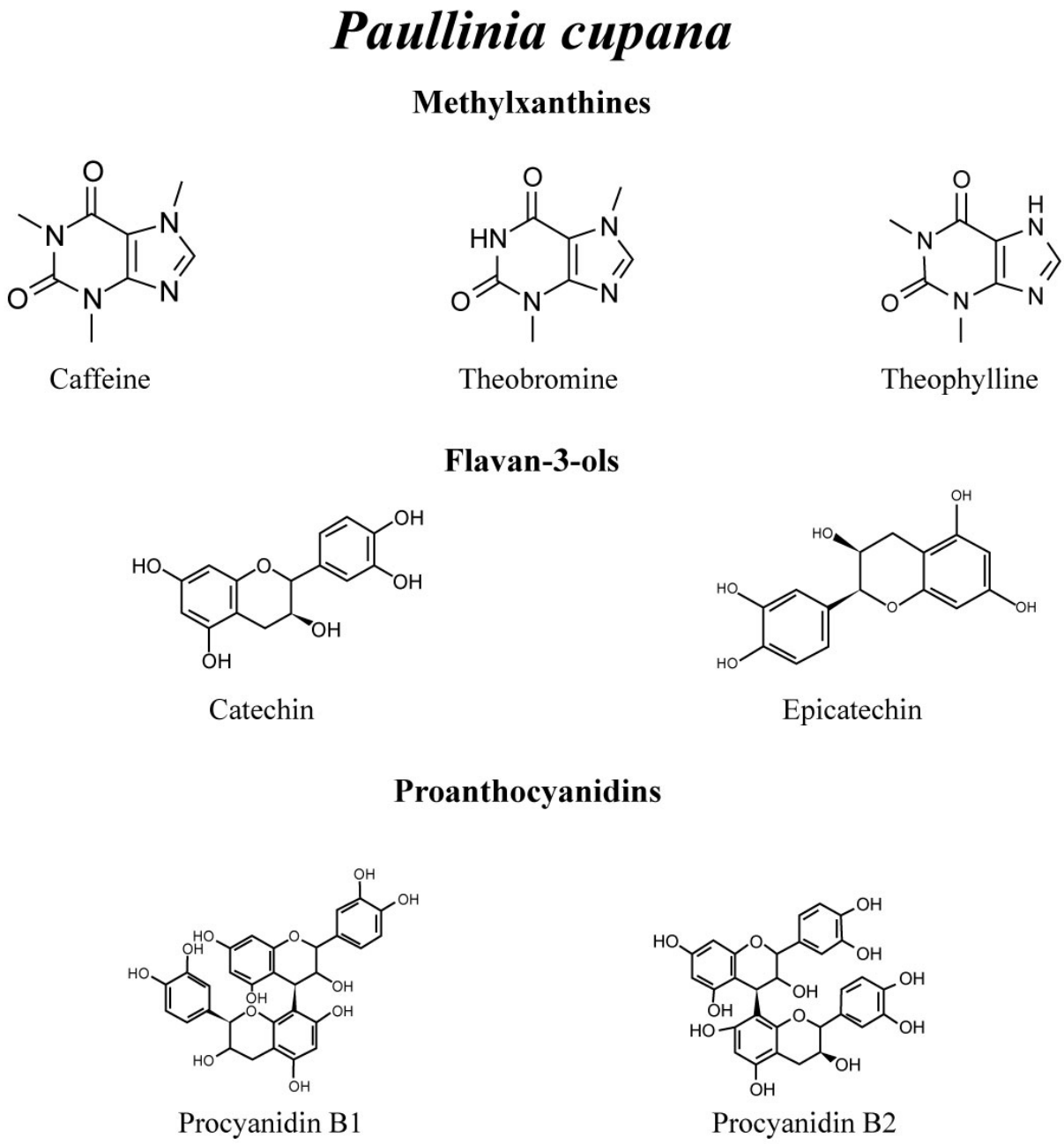

FIGURE 2 - Bioactive compounds from *Paullinia cupana*.

Acai's neuroprotective effects are attributed to its anthocyanins and carotenoids. On one hand, anthocyanins form hydrogen bonds with the polar groups in the lipid-water interfaces of cellular membranes, creating a barrier against reactive oxygen species (ROS) and reactive nitrogen species (RNS), and thus, reducing oxidative damage and inflammation in brain cells (Ma *et al*., 2021; Poulose *et al*., 2014; Saenjum, Pattananandecha, Nakagawa, 2021). On the other hand, carotenoids, which are extremely hydrophobic molecules found in the middle layer of the lipid membrane, scavenge free radicals. This property is in part due to the conjugated double bounds present in these molecules that allow them to accept electrons from reactive species and, therefore, neutralize free radicals. Thus, acai acts as an antioxidant and decreases the susceptibility of the lipid membrane to undergo oxidative damage (Gruszecki, Strzałka, 2005).

The strong antioxidant and anti-inflammatory activities attributed to guarana are related to the condensed tannins (proanthocyanidins, catechin, and epicatechin) (Yonekura *et al*., 2016). Methylxanthines, like caffeine, in guarana are responsible for the stimulating properties and also for the hypolipidemic effect (Lima *et al.,* 2005).

TOXICITY

Ribeiro *et al*. (2010) have demonstrated that acai pulp (3.3, 10.0, and 16.6 g/kg) administered by gavage in Swiss mice does not exert genotoxic effects. These results are in line with the study by Marques *et al*. (2016) that did not find DNA damage in leukocytes, liver, bone marrow, and testicular cells after administering acai pulp (30, 100, and 300 mg/kg) by gavage to rats for 14 days. In addition, clarified acai juice (7 mL/kg) did not alter the generation of ROS and uric acid concentrations in plasma from human volunteers (Mertens-Talcott *et al*., 2008).

Moreover, guarana aqueous extract has low toxicity and is safe in low dosages, even with prolonged consumption. For example, Mattei *et al*. (1998) have reported that either an acute treatment with high doses (2000 mg/kg, i.p. and v.o.) or a chronic one with low doses (3 mg/mL, v.o.) does not exert toxic effects in rats. Also, Espinola *et al*. (1997) have shown that guarana in a single dose (3 and 30 mg/kg) or chronic administration (0.3 mg/mL) presents low toxicity after 23 months. However, Antonelli-Ushirobira *et al*. (2010) have shown that guarana (30 mg/kg) is not toxic to rats, but at higher doses (150-300 mg/kg) it decreases levels of leukocytes and increases levels of alkaline phosphatase and glutamic-pyruvic transaminase (GPT), indicating a possible hepatotoxic effect. An *in vitro* study has shown that a supplement based on guarana, selenium, and L-carnitine (0.04-2.1 mg/mL) does not induce mortality in a leucocyte cell culture model (Teixeira *et al*., 2021).

Taken together these data indicate that açai and guarana extracts have low toxicity, but more pharmacological and toxicological studies are necessary to determine safe dosages, mainly in the form of clinical studies.

THE VALUE OF NATURAL PLANTS AS NEUROPROTECTIVE AGENTS

AD, HD and PD are neurodegenerative diseases characterized by selective and gradual loss of neuronal function (Subhramanyam *et al*., 2019). Features these diseases have in common are the exacerbated accumulation of aggregated proteins, mitochondrial dysfunction, oxidative stress, and neuroinflammation (Singh *et al.,* 2019; Subhramanyam *et al*., 2019). Thus, a lot of attention has been paid to the antioxidant and anti-inflammatory effects of natural products, such as plant extracts (Ahmed *et al*., 2015; Renaud *et al*., 2015).

Plant constituents have been an inspiration for medicinal chemists and a basis for drug development processes for a long time (Newman, Cragg, 2016). From the 1990s to the first decade of the 21st century, the use of plants for drug discovery has decreased, mainly due to new technology overcoming technical barriers, such as high-throughput assays for specific molecular targets, problems associated with the synthesis of natural compounds (Harvey, Edrada-Ebel, Quinn, 2015) and advances in metagenomics and combinational chemistry (Mathur, Hoskins, 2017). Furthermore, there has been rapid improvement in fractionation and recent developments in nuclear magnetic resonance techniques for structural analysis, profile, and isolation, such as HPLC-MS/MS, mass spectrometry, and photodiode arrays for metabolomics (Harvey, Edrada-Ebel, Quinn,

2015). These developments have underpinned renewed efforts to investigate natural plant products and their phytochemical properties (Boasquívis *et al.,* 2018; Machado *et al*., 2016).

Acai (*Euterpe oleracea* Mart.*)* and guarana (*Paullinia cupana* Kunth) are native species from the Amazon Forest (Portella *et al*., 2013) that have shown potential neuroprotective effects in preclinical studies (de Oliveira *et al*., 2019; Zeidán-Chuliá *et al.,* 2013). Both acai and guarana have high antioxidant capacity due in part to their polyphenolic constituents (Portella *et al*., 2013), represented mostly by a large variety of flavonoids (Garzón *et al*., 2017). The main findings from these studies are reviewed below.

METHODOLOGY - LITERATURE SEARCH

We used PubMed database to undertake a bibliographic survey of national and international scientific publications. The following keywords were used: Alzheimer's disease, anti-inflammatory, antioxidant, Huntington's disease, neuroprotection, neuroprotective, mercury, and Parkinson's disease. Each keyword was crossed with *Euterpe oleracea* and *Paullinia cupana*.

Based on the keywords and the scientific name of the fruits, 203 articles were collected after removing the duplicates (the same articles that appeared more than once using the keywords during the search). Of these, from the titles and abstracts, 25 papers were selected for further analysis. Only articles written in English were included and separated into *in vitro* and *in vivo* models of neurodegenerative diseases and neurotoxicity.

EFFECTS OF *EUTERPE OLERACEA* MART - NEUROPROTECTIVE POTENTIAL IN *IN VITRO* MODELS

At a fundamental level, increased levels of Aβ peptide and tau proteins in the brain cause the cholinergic neurodegeneration observed in AD patients (Blanchard, Victor, Tsai, 2022), whereas the dopaminergic neurodegeneration observed in PD patients is triggered predominantly by the toxic accumulation of α-synuclein aggregates in structures known as Lewy bodies (Kulenkampff *et al*., 2021). In addition to the pathological accumulation of aggregated proteins, ROS-induced oxidative damage also plays a role in neurodegenerative diseases. It is well accepted that ROS and RNS cause both oxidative stress and neuroinflammation, followed by DNA damage, protein oxidation, and lipoperoxidation (Saenjum, Pattananandecha, Nakagawa, 2021; Simpson, Oliver, 2020).

In an *in vitro* model of AD using rat phaeochromocytoma (PC12) cells exposed to Aβ1-42 peptide (1.0 μM for 15 min), an aqueous extract of acai (0.5-50 g/mL) significantly improved cell viability and attenuated Aβ1-42 fibrillation and aggregate morphology (Wong *et al*., 2013).

In an *in vitro* model of PD using neuronal-like SH-SY5Y cells exposed to rotenone (5, 15, and 30 nM for 24 h), a hydroalcoholic lyophilized extract of acai (5 μg/mL) showed antioxidant effects (Machado *et al*., 2016). More specifically, rotenone causes mitochondrial complex I (MCI) dysfunction that increases superoxide production and decreases ATP synthesis. This study reported that the acai extract enhanced expression of the MCI subunits, ubiquinone oxidoreductase core subunits S7 (NDUFS7) and S8 (NDUFS8). These subunits assist the assembly of MCI, rebalancing the electron transport chain, decreasing ROS levels, and normalizing ATP synthesis. Due to the oxidative stress, caused by rotenone, there was an increase in lipid peroxidation, which was decreased by the acai extract (Machado *et al*., 2016). In addition, a hydroethanolic extract of acai (0.5, 5.0, and 50 μg/mL) protected SH-SY5Y cells exposed to H2O2 (500 μM for 1 h) (Torma *et al*., 2017), showing an important antioxidant activity of acai extract *in vitro*.

An aqueous extract of acai (0.1 μg/mL) prevented manganese (Mn)-induced oxidative stress (500 μM for 6 h) in primary cultured astrocytes, restoring the reduced glutathione (GSH) / glutathione disulfide (GSSG) ratio and the net glutamate uptake that are impaired in the presence of ROS (da Silva *et al*., 2014). Mn accumulates in the mitochondria, reducing oxidative phosphorylation, increasing ROS, and triggering lipid peroxidation. Therefore, acai was able to protect astrocytic membranes from lipoperoxidation and to decrease Mn-induced

expression of nuclear factor erythroid 2 related factor 2 (Nrf2), which is a transcription factor essential for the transition and activation of genes that contain antioxidant response elements (AREs). Under basal conditions, Nrf2 is inactive due to its cytoplasmic retention by Kelch-like ECH-associated protein 1 (Keap1) and rapid degradation through the ubiquitin-proteasome system. In response to oxidative stress, Nrf2 dissociates from Keap1 and migrates to the cell nucleus, where it stimulates the production of antioxidant enzymes, *e.g.* superoxide dismutase (SOD). Thus, a decrease in Nrf2 expression represents a decrease in oxidative stress (Wardyn, Ponsford, Sanderson, 2015). These data are corroborated by Ajit *et al*. (2016) that have shown that acai extract (6.25 - 50 μg/mL) enhances ARE activity and induces Nrf2 expression in an immortalized rat astrocyte cell line exposed to lipopolysaccharide (LPS) (100 ng/mL for 6 h). The antioxidant potential of aqueous acai extract (1 g/50 mL) was also demonstrated after simulating a reactive environment for oxidation *in vitro*, induced by Fenton's reagent (Vrbovska, Babincova, 2016).

In a model using immortalized murine microglial cells (BV-2) activated by LPS (1 μg/mL for 72 h), a hydroalcoholic lyophilized acai extract (10-1000 μg/mL) reduced ROS levels, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) production and caspase-1 expression at concentrations below 1 μg/mL of extract (de Souza *et al*., 2022). Also, Carey *et al*. (2017) demonstrated a reduction in nitric oxide (NO) production and in the inflammatory cytokine tumour necrosis factor-α (TNF-α) levels in BV-2 cells that were pre-treated with blood serum from rats fed with lyophilized acai pulp (20 g/kg 7 weeks) and then exposed to LPS (100 ng/mL overnight).

Inflammation-mediated neurodegeneration involves microglia activation, which releases neurotoxic and pro-inflammatory factors, including cytokines, such as IL-1β, IL-6, TNF-α, and free radicals, such as H2O2 (Gruendler *et al*., 2020). In addition, activation of inflammatory (*e.g.* caspase-1) and apoptotic caspases (*e.g.* caspases -3 and -8) also occurs (Dhar *et al*., 2019). This suggests that acai has both antioxidant and anti-inflammatory potential, since the decrease in the amount of ROS and RNS (for example, NO) attenuates the activation of inflammatory responses induced by H2O2 and LPS, reducing oxidative stress and, consequently, neuroinflammation and neuronal death (Figure 3).

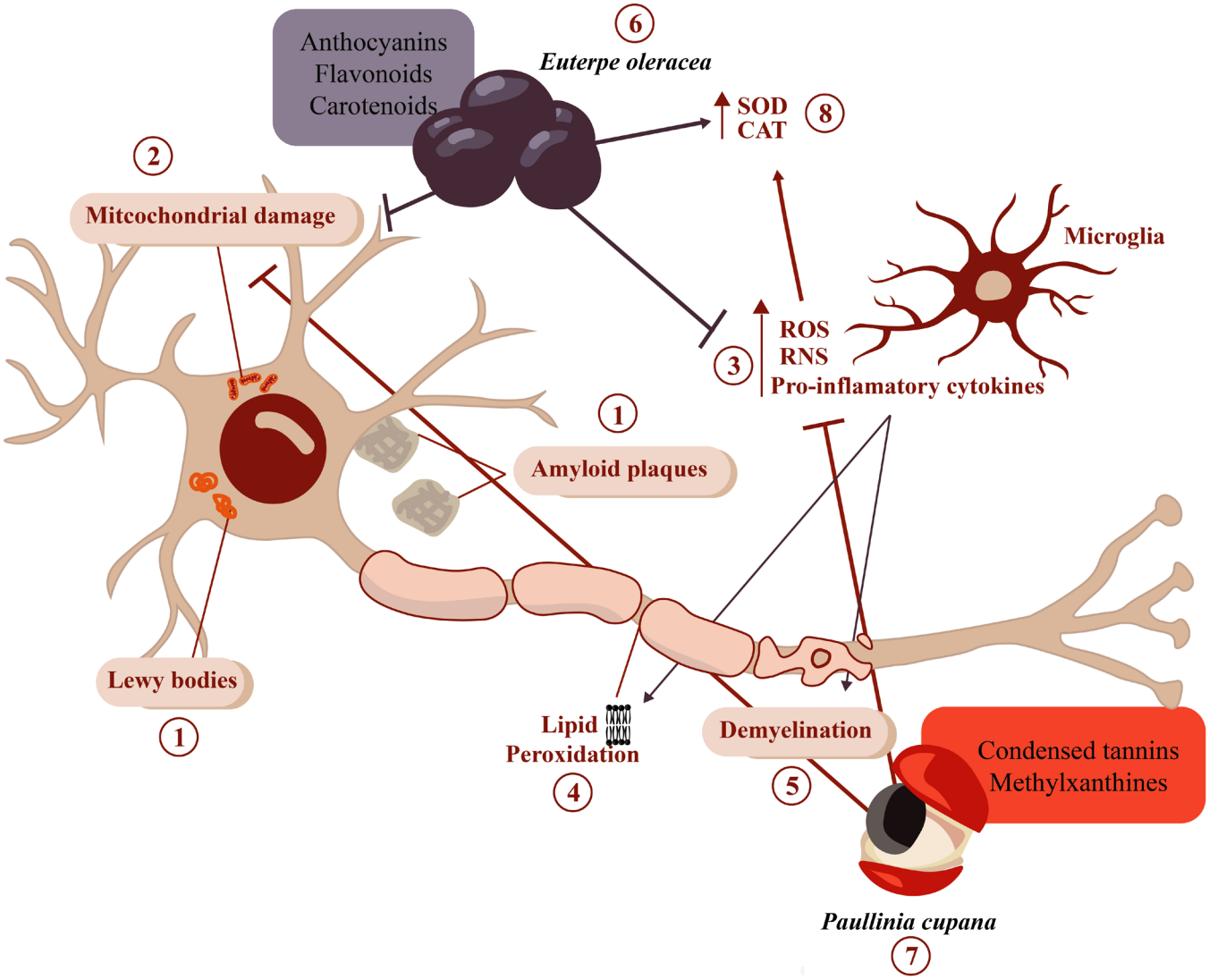

FIGURE 3 - Mechanisms of action of the bioactive compounds found in *Euterpe oleracea* and *Paullinia cupana.* (1) In neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, there is the accumulation of aberrant proteins like amyloid-beta (Aβ) that form the amyloid plaques and α-synuclein that form Lewy bodies, respectively. Also, there is an increase in (2) mitochondrial damage and (3) pro-inflammatory cytokines, reactive oxygen species (ROS) and reactive nitrogen species (RNS) release from the microglia, increasing (4) lipid peroxidation and (5) demyelination, and consequently causing neuronal death. (6) *Euterpe oleracea* and (7) *Paullinia cupana* act as anti-inflammatory and antioxidant agents, decreasing the pro-inflammatory cytokines, ROS and RNS levels, mitochondrial damage, and (8) increasing antioxidant enzymes, such as catalase (CAT) and superoxide dismutase (SOD).

NEUROPROTECTIVE POTENTIAL IN *IN VIVO* MODELS

In *in vivo* models of oxidative damage using H2O2, $O2^{\bullet-}$ and carbon tetrachloride, it has been shown that acai increases the activity of antioxidant enzymes, *i.e.* catalase (CAT) and SOD (Machado *et al*., 2016; Spada *et al.,* 2008).

Frozen acai pulp [40% (weight = volume)], that was mixed with distilled water and then sterilized by filtration before the assay, prevented oxidative damage induced by H2O2 (1 mM) in the cerebellum, cortex, and hippocampus from 10-day-old mice, the brain parts were dissected, homogenized and treated with acai pulp for 30 minutes, and H2O2 was subsequently added to the

mixture (Spada *et al*., 2008). In addition, H2O2-induced oxidative stress triggered SOD and CAT antioxidant activity, which were brought back to basal levels by acai. These data suggest that frozen acai pulp not only protects membranes from lipoperoxidation and H2O2-induced oxidative stress, but also acts similarly to SOD and CAT (Spada *et al*., 2008).

Male Wistar rats treated with acai frozen pulp (7 µL/g, v.o.) daily for 14 days were exposed to the oxidant carbon tetrachloride (3,0 mL/kg, i.p.) in the 15th day. After 4 hours levels of pro-inflammatory cytokines, such as IL-1β, IL-18, and TNF-α, were lower in the cerebral cortex, hippocampus, and cerebellum of animals treated with acai compared to controls (Machado *et al*., 2015).

Moreover, lyophilized acai powder added to rodent chow (20 g/kg 6 weeks) reduced pro-oxidants NADPH-oxidoreductase-2 (NOX2) and transcription factor NF-κB, as well as increased Nrf2 expression levels in the cortex and hippocampus from 19-month-old rats (Poulose *et al*., 2017). ROS are known to cause microglial overactivation that leads to an increase in NF-κB transcripts and production of pro-inflammatory cytokines (*e.g.* IL-6 and TNF-α) and enzymes, such as NOX2, can modulate ROS and RNS (for example, $O2^{\bullet-}$ and NO) increase (Gage, Thippeswamy, 2021; Park *et al*., 2008; Singh *et al*., 2019). Transcription factors related to antioxidant responses, such as Nrf2, can attenuate inflammatory processes due to their indirect negative effect on ROS production (Wardyn, Ponsford, Sanderson, 2015).

ANTIDEPRESSANT AND ANTI-AGING POTENTIAL

Depression is a mental disorder that represents an important and growing public health problem, with approximately 300 million people of all ages affected worldwide. Depressed humour, anhedonia, guilt feeling, low self-esteem, as well as sleep and appetite disorders, characterize this neurological condition, creating a significant impact on the individual's quality of life (WHO, 2021). Furthermore, depression is positively correlated with neurodegenerative diseases, such as AD and PD. Neuronal structures and functions are compromised in these diseases, and the impairment of certain brain networks leads to the development and worsening of a depressive condition (Réus *et al*., 2016).

Accelerated aging has been demonstrated in patients with depression, characterized by a significant decrease in telomere length and telomerase reverse transcriptase (TERT) expression (Lin, Huang, Hung, 2016; Vance *et al*., 2018). A study using a depressive-type behaviour model induced by the administration of LPS (0.5 mg/kg, i.p.) in mice has demonstrated that clarified acai juice (10 µL/g of body weight) significantly protects hippocampal cells and prevents neuronal loss. In addition, acai significantly increased TERT mRNA expression and 4 doses of clarified acai juice were sufficient to completely abolish the despair and anhedonia behaviours (Souza-Monteiro *et al*., 2019). These findings are reinforced by a review suggesting that dietary consumption of foods rich in flavonoids, such as acai, could attenuate neurodegeneration and prevent or reverse age-dependent cognitive decline (de Oliveira *et al*., 2019).

EFFECTS OF *PAULLINIA CUPANA* KUNTH - NEUROPROTECTIVE POTENTIAL IN *IN VITRO* MODELS

It has been reported that guarana powder can significantly reduce Aβ aggregation in a concentration-dependent manner, from 100% in the concentration of 10 µg/mL to 29% in the concentration of 1000 µg/mL in SH-SY5Y cells. Furthermore, guarana was able to prevent the cytotoxicity induced by advanced glycation end-products, such as methylglyoxal (350 µM), glyoxal (600 µM), and acrolein (20 µM). These molecules are irreversible adducts that accumulate in the aging brain and are known to promote Aβ aggregation (Bittencourt *et al*., 2014).

In an *in vitro* PD model, guarana powder (0.312 and 0.625 mg/mL) protected SH-SY5Y cells against rotenone-induced cytotoxicity (300 nM 48 h), as measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (de Oliveira *et al*., 2011). Since rotenone affects MCI proteins, it could be speculated that the protective effects of guarana powder were, in part, due to the renormalization of the activity of the electron transport chain. However, more studies are necessary to confirm this hypothesis.

Vincristine is a drug widely used for the treatment of different types of cancer, mainly leukemia (Dumontet, Jordan, 2010). In addition, vincristine increases ROS production and causes a cellular imbalance in different brain regions in rats, via lipoperoxidation (Martins *et al*., 2011), indicating a close relationship between vincristine and oxidative stress, since ROS is a major contributor to neurodegeneration. In a study, using cerebral and cerebellar cells from mice exposed to vincristine (0.009 μM for 24 h and 0.0007 μM for 72 h), the hydroalcoholic extract of guarana (10, 30, 100 and 300 μg/mL) increased cell viability by stimulating CAT activity (10, 30 and 100 μg/mL), as well as reducing ROS and lipoperoxidation levels (Veloso *et al*., 2017) (Figure 3).

In addition to its effects on oxidative stress, the hydroalcoholic extract of guarana (1, 5, 10 and 20 mg/mL) reduced the levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), caspase-1, caspase-3 and caspase-8 in SH-SY5Y cells exposed to methylmercury (MeHg) (6 μM 72 h) (Algarve *et al*., 2019).

NEUROPROTECTIVE POTENTIAL IN *IN VIVO* MODELS

C. elegans is a nematode of the Rhabditidae family used to model neurodegenerative diseases due to its highly conserved transcription factors that regulate responses to stress resistance, longevity, and protein homeostasis, allowing the elucidation of their roles in the toxicity of proteins and neurodegeneration (Dimitriadi, Hart, 2010). Specifically, transgenic models of C. elegans can induce the expression of human Aβ protein (McColl et al., 2012) and polyQ chains, a portion of mutant huntingtin (mHTT) formed by glutamine repeats (Dimitriadi, Hart, 2010). In addition, transcription factors, such as DAF-16 (ortholog of FoxO proteins in mammals), SKN-1 (ortholog of mammalian factor Nrf2), and HSF-1 (ortholog of HSF2 in humans), play essential roles in attenuating Aβ aggregation, toxicity and polyQ formation (Brunquell *et al*., 2018).

To our knowledge, three studies using *in vivo* models have demonstrated the cytoprotective effects of guarana. In the first one, guarana-induced resistance to stress was dependent on the transcription factor DAF-16 (Peixoto *et al*., 2017). Under stress conditions, DAF-16 migrates to the cell nucleus and activates the transcription of several genes responsible for the response against stressors, such as CAT, SOD-3, and heat shock protein 16.2 (HSP-16.2), a chaperone that prevents incorrect protein folding (Fonte *et al*., 2002). This suggests that guarana cytoprotective effects are in part due to the expression of protective genes. In addition, the aqueous extract of guarana (300 μg/mL) was able to reduce the formation of polyQ aggregates expressed in C. elegans muscle.

In C. elegans models for AD, expressing Aβ1-42, and HD, expressing a polyQ beam of mHTT, it has been demonstrated that the hydroalcoholic extract of guarana (10-50 mg/mL) delays Aβ-induced paralysis, reduces polyQ aggregation in muscle, and increases SOD-3 and HSP-16.2 expression (Boasquívis *et al*., 2018). In addition, an ethanolic extract of guarana (1 mg/mL) decreased Aβ aggregation in Aβ1-42-expressing C. elegans, as well as attenuated Aβ-induced oxidative damage due to increased HSP-16.2 expression (Zamberlan *et al*., 2020).

All these studies on acai and guarana neuroprotective properties are summarised in Tables I and II, and their beneficial actions as antioxidant and anti-inflammatory agents are summarized in Figure 4.

TABLE I - Neuroprotective effects of acai in preclinical studies using neurodegenerative disease and neurotoxicity models

Model	Presentation	Dosage	Main effects	Reference
In vitro studies				
PC12 cells exposed to Aβ	Aqueous extract	0.5-50 g/mL	Increased cell viability and inhibition of Aβ1-42 aggregation	Wong *et al*., 2013

TABLE I - Neuroprotective effects of acai in preclinical studies using neurodegenerative disease and neurotoxicity models

Model	Presentation	Dosage	Main effects	Reference
Primary astrocytes exposed to Mn	Aqueous extract	0.1 µg/mL	Prevention of oxidative stress and protection against LPO	da Silva *et al*., 2014
DI TNC1 astrocytes exposed to LPS	Lyophilized powder	6.25-50 µg/mL	Regulation of Nrf2/ARE-mediated responses	Ajiti *et al.*, 2016
SH-SY5Y cells exposed to rotenone	Aqueous extract	5 µg/mL	Increased MCI content and activity, through NDUFS7 and NDUFS8 overexpression and decreased ROS and LPO levels	Machado *et al*., 2016
Oxidation-induced liposome-rich environment	Aqueous extract	1g/50 mL	Cell-membrane protection against free radicals	Vrbovská, Babincová, 2016
BV-2 microglial cells	Pulp	20 g/kg for 7 weeks	Reduction of TNF-α levels	Carey *et al*., 2017
SH-SY5Y cells exposed to H2O2	Hydroalcoholic extract	50 µg/mL	Cytoprotection (13 - 62%)	Torma *et al.,* 2017
LPS-activated BV-2 microglial cells	Hydroalcoholic lyophilized extract	10-1000 µg/mL	Reduction of ROS, pro-inflammatory cytokines and caspase-1 levels	Souza *et al*., 2020
In vivo studies				
Wistar rats (10-day-old) exposed to H2O2	Frozen pulp	40% (weight = volume)	Reduction of H2O2-induced damage and CAT and SOD activities	Spada *et al*., 2009
Male Wistar rats (90-day-old) exposed to CCl4	Pulp	7 µL/g for 14 days	Prevented inhibition of CK, TBARS, carbonyl and CAT activity in cerebral cortex, hippocampus and cerebellum	de Souza *et al*., 2015
Elderly mice (19-week-old)	Lyophilized powder	20 g/kg for 6 weeks	Reduced NOX2 and NF-κB pro-oxidants and increased Nrf2 expression in cortex and hippocampus	Pulouse *et al*., 2017
Male Swiss rats exposed to LPS	Clarified juice	10 µL/g of body weight for 4 days	Prevented neuronal loss associated with the depressive-like state. Increased TERT mRNA expression. Abolished despair and anhedonia behaviours.	Souza-Monteiro *et al.,* 2019

Abbreviations: ARE: antioxidant response element; CAT: catalase; CCL4: carbon tetrachloride; CK: creatine kinase; H2O2: hydrogen peroxide; LPO: lipoperoxidation; NDUFS7: NADH: Ubiquinone Oxidoreductase Core Subunit S7; NDUFS8: NADH: Ubiquinone Oxidoreductase Core Subunit S8; NOX2: NADPH oxidase 2; Nrf2: nuclear erythroid-related factor 2; ROS: reactive oxygen species; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TERT: telomerase reverse transcriptase.

TABLE II - Neuroprotective effects of guarana in preclinical studies using neurodegenerative disease and neurotoxicity models

Model	Presentation	Dosage	Main effects	Reference
In vitro studies				
SH-SY5Y cells exposed to rotenone	Powder	0.312 and 0.625 mg/mL	Significant increase in cell viability	Oliveira *et al*., 2011
SH-SY5Y cells exposed to Aβ, MGO, GO and ACR	Powder	10, 100, 1000 µg/mL	Reduced Aβ1-42 aggregation, prevented MGO, GO and ACR-induced cytotoxicity	Bittencourt *et al*., 2014
Mouse brain and cerebellum exposed to VCR	Hydroalcoholic extract	10, 30, 100, 300 µg/mL	Increased cell viability, stimulating CAT activity, reducing ROS and LPO levels	Veloso *et al*., 2017
SH-SY5Y cells	Hydroalcoholic extract	1, 5, 10, 20 mg/mL	Reduced IL-1β, IL-6, TNF-α, caspase-1, caspase-3, caspase-8 levels	Algarve *et al*., 2019
In vivo studies				
C. elegans expressing Htn-Q40	Aqueous extract	300 µg/mL	Reduced the formation of polyQ aggregates	Peixoto *et al*., 2017
C. elegans expressing Aβ1-42 and Htn-Q150	Hydroalcoholic extract	10-50 mg/mL	Protected against polyQ and Aβ1-42 toxicity. Increased expression of SOD-3 and HSP-16-2	Boasquívis *et al*., 2018
C. elegans expressing Aβ1-42	Ethanolic extract	1 mg/mL	Reduced Aβ aggregation and Aβ-induced oxidative damage through HSP-response activation	Zamberlan *et al*., 2020

Abbreviations: ACR: acrolein; Aβ: amyloid-beta; CAT: catalase; GO: glyoxal; HSP: heat shock protein; LPO: lipoperoxidation; MGO: methylglyoxal; polyQ: polyglutamine chain; ROS: reactive oxygen species; SOD: superoxide dismutase; VCR: vincristine.

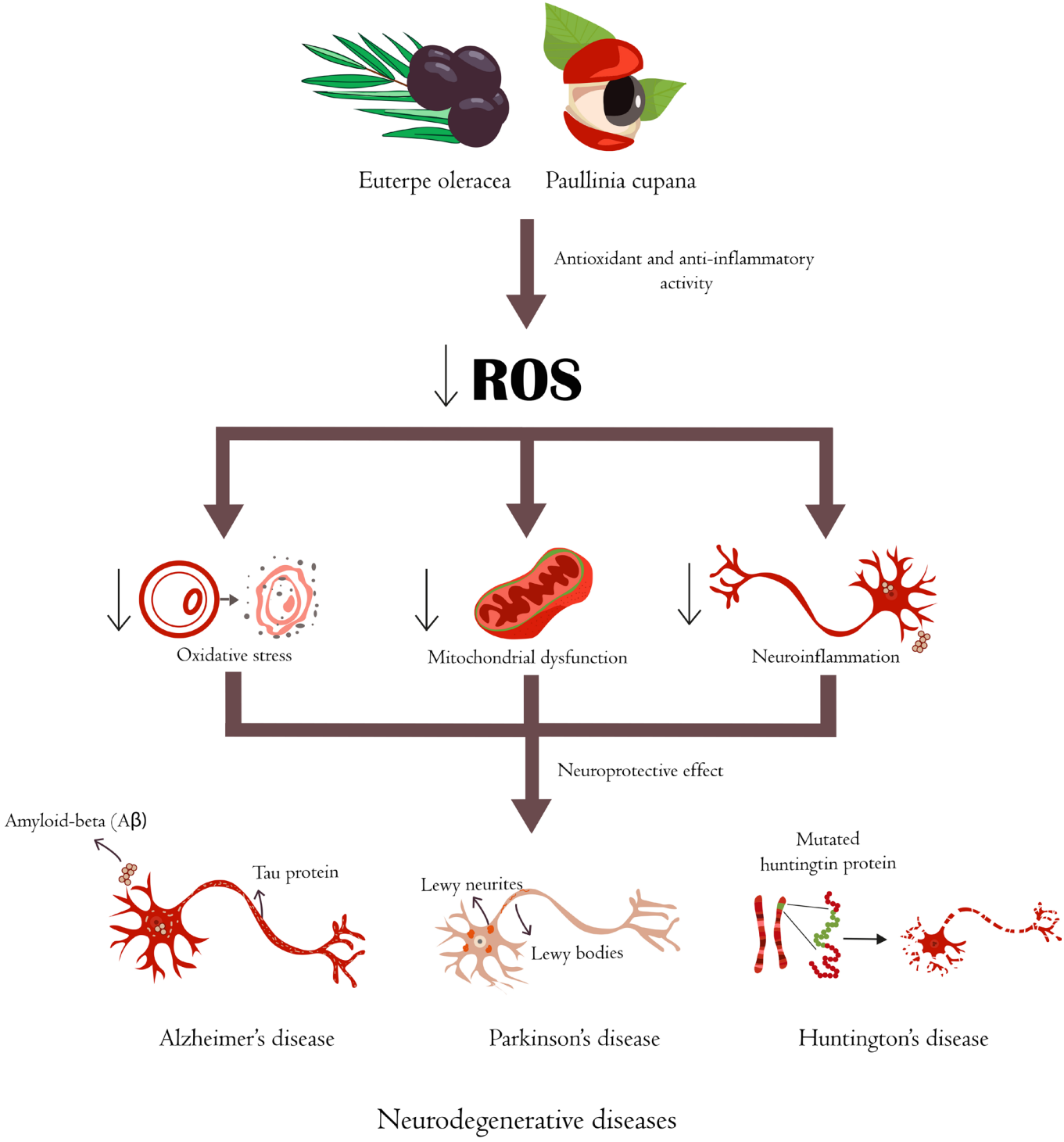

FIGURE 4 - *Euterpe oleracea* and *Paullinia cupana* as neuroprotective agents. The chemical compounds found in these fruits, such as flavonoids, decrease reactive oxygen species (ROS) levels and, consequently, prevent oxidative stress, mitochondrial dysfunction, and neuroinflammation, leading to neuroprotection in *in vitro* and *in vivo* models of Alzheimer's, Parkinson's and Huntington's diseases.

CONCLUSIONS

The molecular mechanisms of phytochemicals, such as flavonoids, include the prevention of oxidative damage and suppression of inflammatory response, which are pathophysiological characteristics present in several neurodegenerative diseases. The studies reviewed here suggest that these molecules, which are present in acai and guarana, hold the potential for preventing and/or treating neurodegeneration, as well as a therapeutic adjuvant for depression and slowing down the physiological aging process.

Both acai and guarana, whether in powder, pulp, juice, ethanolic, or lyophilized hydroalcoholic extract, have shown promising neuroprotective effects in *in vitro* and *in vivo* models of neurodegenerative diseases. In addition, acai berry has demonstrated antidepressant and anti-aging potential. However, there is a need for further pre-clinical and then clinical studies so that these fruits could be validated as new pharmacological therapies. For example, before acai and guarana can be considered as drug candidates, studies that prove their safety and efficacy, as well as their possible adverse effects, bioavailability in different forms of administration, characterization of individual properties, and, mainly, of flavonoid dosages, should be performed. These data are essential to guide the formulation of new therapies to prevent and/or treat diseases that have oxidative stress and neuroinflammation as part of their pathophysiologies, such as AD, HD, and PD. The data reviewed here reinforces the potential that the Amazon Forest holds to provide neuroprotective agents and highlights these fruits as drug candidates for future clinical research.

CONFLICT OF INTERESTS

None.

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AUTHOR CONTRIBUTIONS

The review was conceived and designed by G.N.C., L.Y.Q., and H.I.C. Data collection and draft of the manuscript were performed by G.N.C., L.Y.Q., and I.N.S. The critical revision was made by H.I.C. All authors revised and approved the final version of the manuscript.

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