Anticonvulsant properties of *Euterpe oleracea* in mice


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**Abstract**

Açai (*Euterpe oleracea* Mart.), a highly consumed fruit in Amazon, is from a common palm with remarkable antioxidant properties. Because oxidative stress and seizures are intimately linked, this study investigated the potential neuroprotective and anticonvulsant effects of commercial clarified açai juice (EO). EO did not alter spontaneous locomotor activity. Four doses of EO were sufficient to increase latencies to both first myoclonic jerk and first generalized tonic-clonic seizure and significantly decrease the total duration of tonic-clonic seizures caused by pentylentetrazol administration. Also, electrocortical alterations provoked by pentylentetrazol were prevented, significantly decreasing amplitude of discharges and frequencies above 50 Hz. EO was also able to completely prevent lipid peroxidation in the cerebral cortex, showing a potent direct scavenging property. These results demonstrate for the first time that *E. oleracea* significantly protects against seizures and seizure-related oxidative stress, indicating an additional protection for humans who consume this fruit.

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**1. Introduction**

Seizures result from isolated responses in the brain to acute neurological insults or alterations of homeostasis in acute diseases, such as stroke and head trauma. Seizures are the major hallmark of epilepsy, and the pathology is characterized by unprovoked and spontaneous recurrent events. Clonic and tonic-clonic seizures are considered the most serious types of epileptic episodes, definitively affecting the quality of life of patients and significantly increasing mortality due to this pathology.

Approximately 50 million people worldwide are affected by epilepsy and approximately 80% of them are from developing countries, such as Brazil (WHO, 2012). Major concerns in this pathology are refractory epilepsy, as seizures are not controlled with current anticonvulsant pharmacotherapy in nearly 30% of patients, and difficulties accessing adequate treatment (Sneker and Fountain, 2003). In developing countries, almost three out of four patients do not receive this treatment (WHO, 2012). Therefore, new proposals of therapy based on bioactive compounds in the diet or plants become realistic alternatives to prevent, stop, or even reverse the events surrounding seizures and epilepsy (Puttachary et al., 2015; Sharma and Jain, 2014; Zhu et al., 2014).

One of the fruits highly consumed in the Amazon is açai, which shows remarkable antioxidant properties (Gordon et al., 2012; Kang et al., 2011). Açai, or açai drink, is made from the fruit of a very common palm in the eastern Amazonian floodplains (*Euterpe oleracea* Martius, family Arecaceae). Clarified açai is largely

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**Abbreviations:** EO, clarified açai (*Euterpe oleracea*) juice; ILAE, International League Against Epilepsy; DM, dry matter; PTZ, pentylentetrazol; DPH, 1,1-diphenyl-2-picrylhydrazyl; MDA, malondialdehyde; EEG, electroencephalogram; ECoG, electrocorticogram.

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available on the international market (Bichara and Rogez, 2011) which shows remarkable antioxidant properties.

Oxidative stress and seizures are intimately linked. In addition to behavioral changes, seizures promote oxidative stress in both animal models of seizures and patients with epilepsy (Aguir et al., 2012; Puttachary et al., 2015). Oxidative stress is an imbalance between the generation of oxidant compounds and the activities of antioxidant defense systems, resulting in an overproduction of reactive oxygen species (Aguir et al., 2012; Cardenas-Rodriguez et al., 2013; Puttachary et al., 2015). In addition to contributing to neuronal hyperexcitability and macromolecules (protein, DNA, lipids) damage, oxidative stress plays a major role in refractory epilepsy in experimental models and humans (Aguir et al., 2012; Cardenas-Rodriguez et al., 2013). During the last decade, different antioxidants have been proposed as new therapeutic tools against seizures and epilepsy with a focus on natural products because they are naturally present in human food or folk medicine (Puttachary et al., 2015). Thus, some flavonoids presented in açai, such as wogonin, fisetin, vitexin, and rutin, have already showed their efficacy to prevent seizures in experimental models with PTZ (Zhu et al., 2014).

Therefore, this study aimed to investigate the potential neuroprotective and anticonvulsant effect of clarified açai (E. oleracea) juice (EO) in an experimental model of seizures.

2. Materials and methods

21. Animals and ethical aspects

Male Swiss mice (250±35 g) were maintained in a controlled environment (21 ± 2 ºC; 12 h light/dark cycle) with access to food and water ad libitum. All experimental procedures were approved by the Committee for Ethics in Experimental Research with Animals of the Universidade Federal do Pará (license number B10197-14) and followed the guidelines suggested by the NIH Guide for the Care and Use of Laboratory Animals. A total number of 68 animals were used in the present study: 20 for open field test, 32 for convulsive behavior and biochemical tests and 16 for electrocorticographic recordings. Animals were randomly grouped and the exact number of animals for each group can be found in the legend of figures. Animals for electrocorticographic recordings were submitted to surgical procedures before any treatment (see section 2.6). No animal died naturally (without euthanasia) from all treatments carried out in the present study. All efforts were carry out to reduce the number of animals and to minimize their suffering.

22. Clarified açai (E. oleracea Mart.) juice (EO)

Plants were identified as E. oleracea Martins (Arecales) by comparing with a voucher specimen (#268543) deposited in the Herbarium of Instituto Nacional de Pesquisas da Amazônia (INPA, Brazil). Samples of clarified açai juice were kindly provided by Amazon Dreams (Belem, Pará, Brazil). This juice was produced by a patented process licensed by both Amazon Dreams and Universidade Federal do Pará (PI 1004060-3) that consisted of micro-filtration and centrifugation of an açai juice prepared with fresh fruits. Consequently, the final product contained no lipids, proteins, or fibers (total solids < 1% DM) and constitute an ideal model for evaluating the impact of phenolic compounds (>1400 mg gallic acid equivalents/l).

23. Treatments

All animals were treated (10 ml/g body weight) with EO or saline by gavage once a day for four days. One hour after the last dose of EO or saline, a set of 20 animals (control and EO groups) were evaluated with open field test to analyze possible alterations of spontaneous locomotor activity due to EO treatment. At the same time (also 1 h after the fourth dose of EO or saline), all the other animals were injected intraperitoneally with only one dose of pentylenetetrazol (PTZ; 60 mg/kg) or saline (Pires et al., 2012) and behavioral analyses of seizures or electrocorticographic recordings were carried out with continuous monitoring.

24. Open field test

Analysis of spontaneous locomotor activity with the open field test was carried out between 8:00±12:00 a.m. The animals were placed in a wooden box (with floor divided by black lines into 12 equal quadrants) and they were observed for 5 min. Number of crossed quadrants (crossings) and fecal bolus and behaviors of rearing and grooming were recorded as described elsewhere (Rodrigues et al., 2012).

25. Behavioral analyses of seizure

After PTZ injection, animals were continuously monitored for 20 min. Latencies to first myoclonic jerk and first generalized tonic-clonic seizure, as well as the total duration of tonic-clonic seizures, were recorded (Souza et al., 2013). The animals were then sacrificed by cervical dislocation and the cerebral cortex homogenized and stored at 4 ºC to analyze lipid peroxidation.

26. Surgical procedures

A different set of animals (n=46) was anesthetized with xylazine (5 mg/kg i.p.) and ketamine (80 mg/kg i.p.) and immobilized in a stereotaxic apparatus. After subcutaneous application of lidocaine 2%, electrodes (1 mm diameter) were implanted 1 mm posterior to the bregma, ±1 mm lateral (both hemispheres). Electrodes were fixed in the dura mater and isolated with dental autopolymerized acrylic. Animals were then monitored every 6 h and allowed to recovery from surgery for 2 days, before treatment with EO or saline as described above.

27. Electrocorticographic recordings

On the last day of treatment, the electrodes of each animal were connected to a data acquisition system (high-impedance amplifier, Grass Technologies, P511; coupled to an oscilloscope, Protek, 6510). The recording electrode was located on the right side of the hemisphere, and the electrode on the left side was used as a reference. The whole experiment was performed in Faraday cages. Data were monitored continuously with a range of 1 KHz (National Instruments, Austin, TX) and analyzed using LabVIEW Express software.

After 10 min of accommodation, the baseline of each animal was recorded for 30 min and then PTZ (60 mg/kg i.p.) injected as described above. Recording was continued for another 30 min.

Data were graphically expressed showing differences in potential between the two electrodes (reference and recording). Spectrograms were calculated using a Hamming window of 256 points (256/1000 s), and each frame was generated with an overlap of 128 dots per window. For each frame, the power spectral density (PSD) was calculated with the Welch average periodogram method. Frequency histograms were generated with the PSD of the signal (with 1 Hz boxes).
28. Assay of direct free radical scavenging

To evaluate the possibility of direct free radical scavenging by EO, we used the protocol described by Gulcin et al. (2004). Briefly, dilutions of EO (1:10, 1:100, 1:1000) were added to a solution of 40 mg/ml 1,1-diphenyl-2-picrylhydrazyl (DPPH) in ethanol. After 30 min of incubation in darkness at room temperature, absorbance was measured at 517 nm and the percentage of scavenged DPPH molecules calculated according to the following formula:

\[% \text{ scavenged } \text{DPPH} = \frac{A_0 - A}{A_0} \times 100;\]

where \(A_0\) is the absorbance of the control group and \(A\) is the absorbance in the presence of EO.

29. Quantitation of lipid peroxidation

Lipid peroxidation in the cerebral cortex samples was spectrophotometrically assessed using malondialdehyde (MDA) as an indicator (Esterbauer and Cheeseman, 1990). Briefly, after centrifugation of the samples at 2500 g for 10 min, a solution containing methanesulfonic acid and N-methyl-phenyl indole (10.3 mM in acetonitrile) diluted in methanol (1:3) was added to the supernatants and incubated for 40 min at 45 °C. Absorbance was measured at 570 nm and compared to standard concentrations of MDA. The lipid peroxidation values were corrected for the protein concentration of each sample and expressed as nanomoles MDA per milligram of protein.

30. Total protein content

Total protein content was determined in all samples as described elsewhere (Bradford, 1976). Aliquots of the homogenates were incubated with Bradford reagent (5% ethanol, 8.5% phosphoric acid, 0.25% Coomassie Brilliant Blue G-250) for 2 min at room temperature. The absorbance of each sample was measured at 595 nm and compared to standard solutions of bovine serum albumin.

31. Statistical analysis

Statistical analysis was performed using the software Graph Pad Prism (version 5.0). Initially, the Gaussian distribution of the data was tested by the Kolmogorov-Smirnov test. Non-parametric data for behavioral parameters (latencies and duration of seizures) were expressed as median ± interquartile range and analyzed using the Mann-Whitney test. Parametric data for open field test, lipid peroxidation, scavenging property, and electrocoricograms (ECoGs) were analyzed by ANOVA followed by Tukey post hoc test when appropriate, and they were expressed as mean ± standard error of the mean (S.E.M). \(P < 0.05\) was considered significant for all analyses.

3. Results

31. Treatment with EO does not affect spontaneous locomotor activity

No statistical differences between animals treated with saline or EO were detected for all parameters analyzed in the open field test (Fig. 1).

32. EO protects against behavioral changes caused by seizures

Only four doses of EO were sufficient to significantly increase the latency to both first myoclonic jerk and first generalized tonic-clonic seizure induced by PTZ (Fig. 2A and B). Treatment with açai also decreased 61% of the time spent in tonic-clonic seizures (Fig. 2C).

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Fig. 1 Treatment with clarified açai (E. oleracea) juice (EO) does not alter spontaneous locomotor activity. EO or saline (SAL) was given by gavage (10 ml/g per day) for 4 days. Data of number of crossed quadrants (A, total crossings), rearing (B), grooming (C), and fecal bolus (D) are mean ± SEM (n = 10). No statistical differences were detected.
Treatment with EO significantly reduces electrical alterations caused by seizures

Animals treated with saline had ECoGs indicating the cerebral activity of environment exploration (irregular pattern of low amplitudes and more frequencies below 10 Hz; Fig. 3). The ECoGs of animals treated with açai were very similar to those of controls (Fig. 3), with low amplitudes and more frequencies below 10 Hz. PTZ provoked a pattern of variable amplitudes with increasing excitability and elicited discharges characteristic of convulsive episodes (Fig. 3). The spectrograms for these animals showed increased frequencies reaching 50 Hz. Treatment with four doses of EO and PTZ led to transitory increases in amplitude, but significantly lower than those provoked by PTZ, pointing to partial inhibition of PTZ effect (Fig. 3). The spectrograms of these latter animals showed energy distributions with few frequencies above 10 Hz.

Regarding the amplitude distributions (Fig. 4), no significant differences were found in the distributions of 1e50 Hz frequencies between animals treated with saline solution or açai (Fig. 4). However, PTZ caused significant increases in amplitudes with a clearly altered distribution pattern, especially for 1e25 Hz frequencies, but it was partially prevented by treatment with EO (Fig. 4). Moreover, quantitation of the amplitudes for each group revealed a significant increase with PTZ, which decreased in approximately 50% by treatment with four doses of EO (Fig. 4).

EO has a high capacity for direct scavenging, preventing the deleterious consequences of oxidative stress caused by seizures in the cerebral cortex

The high antioxidant capacity of açai was detected by the DPPH method (Fig. 5). The direct scavenger property of açai was so potent that a dilution of 1:10 EO was sufficient to cause similar effects as ascorbic acid (1 mg/ml). In addition, PTZ administration provoked a significant increase in lipid peroxidation in the cerebral cortex (Fig. 6), and this effect was completely prevented by treatment with açai.

Discussion

This work demonstrated, for the first time, that E. oleracea juice significantly protects against seizures and seizure-related oxidative stress.

We used an experimental model of seizures with PTZ, a selective blocker of the chloride channel coupled to the GABAα receptor complex. PTZ treatment is an important model of myoclonic and generalized tonic-clonic seizures and is currently considered the gold standard for screening potential anticonvulsant compounds (Loscher, 2011; Pahuja et al., 2012; Souza et al., 2013; Yuen and Troconiz, 2015). Additionally, this model may predict more accurately the physiological consequences of seizures in humans and their responses to treatments when compared with other models (Yuen and Troconiz, 2015).

In our model, commercial samples of EO were used to ensure that the samples were indicative of normal human consumption. Also, clarified juice was chosen because the clarification process eliminates all macronutrients (lipid, fiber, and protein), avoiding possible interference by these compounds in the results. Thus, EO is basically composed of phenolic compounds, with anthocyanins representing a major part of it. Analysis of the samples used in the present study revealed a content of 1662.15 mg gallic acid equivalents/l of phenolic compounds, including 529 mg cyanide equivalents/l of anthocyanins.

Surprisingly, only four doses of EO were enough to significantly increase latencies and strongly reduce the duration of the most serious type of seizures (Fig. 2). Still, electrocorticographic recordings showed that PTZ induced electrical alterations characterized by increased amplitudes and that a previous ingestion of açai prevented these increases in approximately 50% (Figs. 3 and 4).
Electrical recordings, in addition to behavioral evaluation, have been a useful and objective tool for verifying alterations caused by neuronal excitability in both epileptic patients and experimental models. A recent report demonstrated the sensibility of this method for seizures detection and characterization in the PTZ model (Niknazar et al., 2013). This method takes advantages of minimal encephalic damage and is sensitive enough to indicate changes in the severity of crises (characterized by increased frequencies and/or amplitude of waves) that cannot be quantified only with the observation of behavior. In our work, açai partially prevented the alterations caused by PTZ in ECoGs by significantly decreasing both the frequency of discharges and mean wave amplitude (Figs. 3 and 4).

These results are more remarkable when we consider that new therapeutic tools are sometimes proposed as co-adjuvants in polytherapy to improve the effect of classical drugs, but their potency alone is low; this was not the case with açai, because treatment with only the fruit already showed a potent anticonvulsant effect. Moreover, near of 30% of epileptic patients are affected by seizures resistant to current anticonvulsant pharmacotherapy (WHO, 2012), making it essential to find new alternatives, especially those that are easy for isolated populations to access.

The EO dose used in this study (10 ml/g body weight, equivalent to approximately 700 ml for a person of 70 kg) was slightly more than the daily mean human consumption in several regions of Brazil (e.g., in the North, it is not uncommon to find people who consume 1 L/day) and the total concentration of phenolic compounds and anthocyanins is largely representative of those usually measured in açai juice. No changes in body weight (data not shown) or spontaneous locomotor activity (Fig. 1) were detected in animals treated with EO. Moreover, consumption of a similar amount of clarified açai is apparently not toxic for humans (Mertens-Talcott et al., 2008), and acute and subchronic treatments with higher doses of açai pulp do not provoke genotoxic effects in rodents (Ribeiro et al., 2010). Therefore, our results suggest that diet supplementation with EO could have additional value in patients, providing an extra anticonvulsant effect and probably allowing the use of lower doses of classical anticonvulsant drugs, avoiding major
E. oleracea) could be an extremely useful tool for treating seizures, especially in these populations.

What molecular mechanism underlies the potent anticonvulsant effect of açaí? Although a more in depth study is necessary to completely answer this question, the antioxidant capacity of açaí seems to be the first explanation of the anticonvulsant action, because the high phenolic compounds content, such as flavones, which are the main bioactive compounds present in açaí (Dias et al., 2013; Kang et al., 2010, 2011). Direct challenge with DPPH radical revealed a scavenger effect of EO that is at least 10-fold more potent than a solution of 1 mg/ml ascobic acid (Fig. 5). Moreover, an EO dilution of 1:100 demonstrated higher scavenger properties (91.4% of inhibition of DPPH radicals) than 800 mM of Trolox (approximately 81% for the same assay, as described by Bonomo Lde et al. (2014), a compound considered the gold standard in biological assays evaluating antioxidant properties. These results confirm previous studies demonstrating açaí antioxidant capacity (Bonomo Lde et al., 2014; Gordon et al., 2012; Kang et al., 2010, 2011; Xie et al., 2011).

Recent studies support a major role of oxidative stress in the development of epilepsy and epilepsy that is refractory to pharmacological treatment (Aguiar et al., 2012; Cardenas-Rodriguez et al., 2013; Puttachary et al., 2015; Shin et al., 2011). Moreover, classical experimental models of seizures (PTZ, strychnine, and picrotoxin) and epilepsy (pilocarpine and kainic acid) induce seizures via different mechanisms, but share a common oxidative stress pathway (Aguiar et al., 2012; Loscher, 2011).

The role of oxidative stress on seizures in humans has not been fully elucidated and remains controversial (Aguiar et al., 2012; Puttachary et al., 2015; Shin et al., 2011). The brain is extremely vulnerable to oxidative damage, mainly because of weak antioxidant defenses, the increased consumption of oxygen and high oxidable compounds content compared to other organs (Puttachary et al., 2015; Shin et al., 2011). Lipid peroxidation, one of the most deleterious consequences of oxidative stress, is a cascade...
of biochemical events involved in non-specific oxidation of poly
unsaturated fatty acids mediated by free radicals. A significant in
crease in lipid peroxidation has already been shown in both
epileptic patients and experimental models of seizures and epi
lepsy (Aguiar et al., 2012; Puttachary et al., 2015; Shin et al., 2011).

In our work, the administration of 60 mg/kg PTZ significantly
increased lipid peroxidation in the cerebral cortex (Fig. 6). These
results are in accordance with recent studies using the same dose of
PTZ and showing a 44898% increase in lipid peroxidation com
pared to control group (Chowdhury et al., 2013; Naziroglu et al.,
2013). Seizures induced by PTZ exacerbate oxidative stress
through the increased production of ROS and decreased activities of
antioxidant enzymes, such as catalase or superoxide dismutase
(Branco Cdos et al., 2013; Chowdhury et al., 2013; Kumar et al.,
2013; Rodrigues et al., 2014).

Interestingly, açai was able to completely prevent lipid peroxi
dation in the cerebral cortex of animals receiving PTZ (Fig. 6).
Although treatment with açai did not completely eliminate sei
zures, prevention of lipid peroxidation in the cerebral cortex may
lead to a significant reduction in subsequent seizures and their
deleterious consequences, an important concern in epilepsy
patients.

Although our results with the DPPH method and lipid peroxi
dation point to that the scavenger capacity of açai must be a major
responsible for this protection (Figs. 5 and 6), other possible indi
rect mechanisms cannot be discarded. Treatment with açai was
recently shown to modulate the expression of oxidative stress-
related genes, such as gsc1 (the limiting enzyme of glutathione
synthesis), and transcription factors (especially those regulated by
the insulin/IGF-1 signaling pathway) affecting stress resistance
(Bonomo et al., 2014). The possible occurrence of these genetic
mechanisms plus the apparent absence of genotoxic effects of
subchronic treatment with açai (Ribeiro et al., 2010) may be addi
tional support for the use of chronic treatment with açai in epilepsy
patients.

Which components of EO are responsible for eliciting these
possible mechanisms of protection? The relationship between
anticonvulsant and antioxidant activity has been shown by the
induction of anticonvulsant effects through the antioxidant actions
of plant extracts (Naziroglu et al., 2013; Pahuja et al., 2012;
Rodrigues et al., 2012). The anticonvulsant effects of medicinal
plants have been explained based on anxiolytic or sedative prop
erties, the influence on receptors (GABA, glutamate, etc.), and
modulation of neurotropic factors (Zhu et al., 2014). Although
additional behavioral studies are needed, treatment with EO may
not have sedative effects, as no differences were detected in the
open field test (Fig. 1).

The EO used in our work is an aqueous product characterized by
the absence of insoluble solids and lipids while maintaining a high
antioxidant capacity due to the presence of phenolic compounds,
such as anthocyanins, flavones, proanthocyanidins, and other fla
vonoids. Cyanidin-3-rutinoside, cyanidin-3-glucoside, orientin,
husseinorientin, and taxifolin deoxyxheose are the major flavonoids
present in açai (Dias et al., 2012, 2013; Gordon et al., 2012).
Interestingly, recent studies have demonstrated that the major absorp
tion of anthocyanins occurs at the stomach level only 30 min after
consumption (Fernandes et al., 2014). The efficacy of flavonoids,
such as wogonin, fisetin, vitexin, and rutin (one of the most com
mon flavonoids in plants and fruits), has already been shown in
experimental models with PTZ (Zhu et al., 2014).

Independent of the exact composition of EO, the present human
consumption of açai means that additional efforts must be dedi
eated to analyzing the bioactive compounds responsible for these
in vivo effects. Although many in vitro studies have reported the
antiproliferative, anti-inflammatory and cardioprotective effects of
açai (Kang et al., 2011; Moura et al., 2012; Xie et al., 2011), in vivo
studies are still scarce.

5. Conclusions

Despite the other benefits of açai consumption, this work
performed for the first time that clarified E. oleracea juice
significantly protects against seizures and seizure-related oxidative
stress in an in vivo model. The results suggest that regular intake of
açai juice may be an additional protective factor in epilepsy.

Conflicts of interest

Authors declare that no conflict of interests exists. The funders
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