



Antioxidant, Hypoglycemic and Neuroprotective Activities of Extracts from Fruits Native to the Amazon Region: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors equally worked during elaboration of manuscript, as in conceptualization, methodology, formal analysis, data curation, writing (original draft preparation) and writing (review and editing). Also, the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJI/2020/v24i630119

Editor(s):

(1) Dr. Anil Kumar, Devi Ahilya University, India.

Reviewers:

(1) Mastewal Birhan Atanaw, University of Gondar, Ethiopia.

(2) Kumari Shubha, ICAR-RCER, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/61673>

Review Article

Received 28 July 2020
Accepted 03 October 2020
Published 22 October 2020

ABSTRACT

The Amazon forest has the largest biome on the planet, and it is estimated that only 16 to 20% of the identified animal, and plant biodiversity. Considering plant diversity, we will highlight the biological properties of the fruits extracts of Arecaceae, Caryocaraceae, Malvaceae, Myrtaceae, Sapindaceae, and Solanaceae's families due to their significant biological actions. This review presents the antioxidant, glycemic control, and neuroprotective activities from ten fruit extracts distributed in six botanical families in the Amazon region. We obtained 801 publications (described from 2010 to 2020), of which 64 articles were selected by the benchmark previously chosen. The antioxidant effect was the dominant effect observed in the studies used for this review, followed by glycemic control and protective actions in neurons. This review provides a synopsis of the recent literature exploring the extracts from native fruits to the Amazon region that could efficiently prevent pathologies associated with oxidative stress, and cellular maintenance mechanisms.

Keywords: Amazonian extracts; nutrient-rich food; secondary metabolism; biological activities.

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1. INTRODUCTION

Aging and the constant search for a better and healthier life reinforce the appreciation of natural products use as one of the most effective alternatives for scientific research [1]. Brazil is one of the most endowed countries in biodiversity globally, and the Amazon region stands out for the number of exotic fruits considered rich in bioactive substances associated with health benefits [2].

The diversity in the Amazon rainforest represents not only mineral wealth in soil [3] as well as a food source found in animals [4] and plant species [5]. Over time, the man discovered that plant consumption, mostly fruits, had high nutritional value and medicinal effect, currently among the most significant therapeutic agents obtained from nature [6].

Chemical properties of the substances present in these fruits' pulps contain different constituents described in scientific literature as biomolecules capable of altering important cellular metabolic aspects. They have aroused the interest of research groups due to the beneficial properties for human organisms associated with prevention and a lower incidence of chronic and degenerative diseases [7,8].

Researchers have been encouraged to detect substances that can protect cells in the central nervous system. Recent studies suggest that phenolic compounds, flavonoids, carotenoids, terpenes, and inorganic molecules have significant therapeutic actions [9,10,11].

Essential compounds of the Amazon fruits with different proven properties, combined with in vitro and in vivo tests, contribute to the development of new treatments that present zero or significantly reduced adverse effects compared to current therapies. In this review, we compiled the results of scientific studies related to the antioxidant and hypoglycemic activities of Amazonian fruit extracts (10 native plants in 6 botanical families) and their possible contributions to commonly unrelated neuroprotective mechanisms. Thus, encouraging studies of synergistic interaction focused on this thematic.

2. NATIVE PLANTS OF THE AMAZON

Recent studies highlighted changes in consumption by claiming a "nutritional transition"

occurring around the world. Focusing on the research on such a transition in the Brazilian Amazon, recent studies have explored diet changes in rural and traditional populations. Also, certain native fruits have gained a "cultural marker" status. They are wide consumed regardless of the urbanization rates [12] as some botanical families *Arecaceae*, *Caryocaraceae*, *Malvaceae*, *Myrtaceae*, *Sapindaceae*, and *Solanaceae*.

Palms (*Arecaceae*) are monocotyledonous flowering plant, often abundant in tropical and sub-tropical ecosystems with commercially and essential therapeutic species such as coconuts, area nuts, and date palms, as well as a large number of indoor and ornamental species [13]. About medicinal use, *Arecaceae* plants have various therapeutics actions [14]. Traditionally fruits are consumed fresh, boiled, or as juices [15], and some biologically active components included phenolics compounds (catechin, quercetin, gallic acid, rutin, coumaric acid, ferulic acid, chlorogenic acid, quinic acid, caffeic acid, cyanidin-3-O-glucoside, and cyanidin-3-O-rutinoside) [16,17,18,7,19,20], carotenoids (α -carotene, β -carotene, γ -carotene, lycopene, and xanthophylls) [16,7,21,22,20], flavonoids (anthocyanin, luteolin, apigenin, chrysin, myricetin, and kaempferol) [17,19,23] and fatty acids (palmitic and oleic acid) [24]. Some notable species belonging to this majestic plant family include edible and commercially significant members and forest species as *Astrocaryum aculeatum* Meyer, *Bactris gasipaes* Kunth, *Euterpe oleraceae* Mart, and *Mauritia flexuosa* L. f.

Caryocaraceae is a small botanic family with exclusively neotropical distribution (Central and South America), but it is prevalent in the Amazon rainforest. The *Caryocar* genus has sixteen species, some of which have therapeutic [25,26] and economic potential [27], with fruits being a source of edible oil. *Caryocar* species, *Caryocar brasiliense* A.St.-Hil and *Caryocar villosum* (Aubl.) Pers are the most studied species because of the extensive use of its fruit as source nutritious (lipids 51.51%, proteins 25.27%, carbohydrates 8.33%, and fibers 2.2%) and therapeutic purposes. In the Amazonian region, only *Caryocar villosum* (Aubl.) Pers is present, and the local community consumes the pulp fruit for cooking with rice or regional dishes as a substitute for butter and soaps or cosmetic applications [28,27]. Studies have demonstrated the

identification of different compounds, such as phenolic compounds (gallic acid and ellagic acid [28,25] and carotenoids (lutein, antheraxanthin, zeaxanthin, and β -carotene) [6].

Around 1000 species in the world represent the family Malvaceae, distributed widely in tropical and temperate regions. The main spread of these family members, whose majority is widespread, is South America and present almost everywhere except the frigid areas [29]. Compounds from fruits such as flavonoids (flavan-3-ols, procyanidins, flavones, catechin, and epicatechin) [30] and fatty acids: palmitic acid, stearic acid, oleic acid, linoleic acid and α -linoleic acid [31] were characterized. *Theobroma grandiflorum* (Wild. ex Spreng.) Schum. is a Brazilian Amazon rainforest fruit, phylogenetically close to cocoa, with excellent flavor and high agro-economic potential, and the seeds are a product similar to chocolate [31].

The Myrtaceae is a large family of dicotyledonous woody plants containing over 5,650 species organized in 130 to 150 genera. The family is typical in many of the world's biodiversity hotspots such as Southwestern Australia, and the Cerrado and Atlantic Rainforest in Brazil, where up to 90 species of Myrtaceae per hectare can be found [32]. In the Amazon region, *Eugenia stipitata* MacVaugh and *Myrciaria dubia* (HBK) McVaugh have fruits with a significant use history as edible and as traditional medicines [33,34]. Also, compounds like phenolic compounds (gallic acid) and carotenoid (lutein, α -carotene, β -carotene, cryptoxanthin, zeaxanthin, and zeinoxanthin) [33] have identified.

Sapindaceae is a tropical and subtropical family comprising approximately 2000 species, including many economically important species used for their fruits, e.g., guarana (*Paullinia cupana* Kunth), litchi (*Litchi chinensis* Sonn), longan (*Dimocarpus longan* Lour), and pitomba (*Talisia esculenta* (A. St.-Hil.) Radlk.), wood extraction (*Aesculus* sp) or as ornamentals (*Koelreuteuria* sp) [35]. The consumption of *Paullinia cupana* Kunth is commercially exploited mainly by the soft drinks industry. However, it is also highly valued by the cosmetic and pharmaceutical industries [36] primarily by the compounds as phenolic compounds (epicatechin, catechin, and proanthocyanidin) [37,38] and alkaloid (caffeine) [37].

The family Solanaceae has 2,300 species, including many therapeutic (*Solanum sessiliflorum* Dunal) and economically important species, such as tomato, potato, and various peppers. The genus consists of herbs, shrubs, trees, lianas, or rarely epiphytes distributed throughout the world but is most abundant and widely distributed in Latin America's tropical regions, mainly found in the Amazon forest [39,40]. The Solanaceae family is characteristically ethnobotanical and extensively used by humans as food, spice, and medicine [41]. Probably, the therapeutic effects are related to the compounds known as coumarins (p-coumaric acid, p-hydroxydihydrocoumaric acid, vanillic acid, and 5-caffeoylquinic acid) [42,43], flavonoid (naringenin) [42], carotenoids (lycopene, α -carotene, and β -carotene), terpenes (bisabolol, phenylpropene, and apiole), and alkaloid (solasonine) [43].

3. ANTIOXIDANT, HYPOGLYCEMIC, AND NEUROPROTECTIVE EFFECT

In this section, we review our findings at species levels. We discuss current scientific evidence that might explain the uses of the extracts of fruits on the Amazon region to antioxidant, hypoglycemic, and neuroprotective actions (Table 1).

Antioxidants are molecules that can control the production of free radicals in living organisms, which may have an endogenous (superoxide dismutase, catalase, glutathione reductase, and other enzymes) or exogenous (through food, like tocopherols, ascorbic acid, polyphenols, selenium, and carotenoids) origins [44,45]. A free radical typically is defined as any species capable of independent existence (hence the term "free") containing one or more unpaired electrons. Once derived from oxygen or nitrogen metabolism, they are known as reactive oxygen species (ROS) or reactive nitrogen species (RNS) that could attack the essential molecules in the cell, resulting in several cellular damages, such as DNA oxidation or the lysis of biological membranes [46,44].

The antioxidant acts as scavengers or neutralizers of ROS or RNS, making them potential agents to prevent oxidative stress, thereby playing a therapeutic role in various diseases including cancer, diabetes, and neurodegenerative diseases as well as aging [47].

Table 1. Bioactive compounds with antioxidant, hypoglycemic and neuroprotective action (*in vitro* and *in vivo* studies)

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
<i>Astrocaryum aculeatum</i> Meyer (Tucumã)	Arecaceae	Pulp and peel	Phenolic compound: catechin [7], quercetin, gallic acid, rutin [7, 20], chlorogenic acid [20] and caffeic acid [7]. Carotenoids: β -carotene [7, 20]. Fatty acids: Palmitic and Oleic acid [24].	<i>in vitro</i> : Murine macrophage RAW 264.7 cells culture were protected by ethanolic extracts at 30 μ g/mL exposed to PHA [7]. Scavenging ROS in human lymphocytes exposed to H ₂ O ₂ with IC ₅₀ 11.24 μ g/mL for ethanolic pulp extract and 8.98 μ g/mL for ethanolic peel extract [20]. TRAP: 102.38 \pm 4.8 μ g/mL and 224.57 \pm 3.9 ng/mL for ethanolic peel and pulp extracts [20]. <i>in vivo</i> : The oil was obtained by hydraulic pressing and mice were protected at 500, 1,000 and 2,000 mg/kg b.w. exposed to DXR [52].	<i>in vitro</i> : α -amylase (IC ₅₀ 2.9 mg of sample dw/mL of reaction) and α -glucosidase (IC ₅₀ 1.7 mg of sample dw/mL of reaction) inhibitory activity of polyamide-purified extracts obtained by solid-phase extraction of native fruits and commercial frozen pulps [60]. <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
<i>Bactris gasipaes</i> Kunth (Pupunha)	Areaceae	Pulp	Carotenoids: α -carotene [22], β -carotene [16, 22], γ -carotene; lycopene, and xanthophylls [22].	<i>in vitro</i> : Scavenging ROS 11.6 ± 0.2 and 9.1 ± 0.3 μg carotenoids/mL for Yurimaguas and Ecuador aqueous extract varieties, respectively [96]. <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R
<i>Caryocar villosum</i> (Aubl.) Pers (Piquiá)	Caryocaraceae	Pulp and peel	Phenolic compound: gallic acid and ellagic acid [25, 28]. Carotenoids: lutein, antheraxanthin, zeaxanthin and β -carotene [6].	<i>in vitro</i> : Scavenging ROS (IC_{50} 1.7 to 108 $\mu\text{g}/\text{mL}$) and RNS (IC_{50} 0.05 to 0.59 $\mu\text{g}/\text{mL}$) at hydroethanolic extract [6]. Scavenging ROS IC_{50} 8.52 ± 0.37 $\mu\text{g}/\text{mL}^{-1}$ at shell hydroethanolic extract and IC_{50} 8.48 ± 0.49 $\mu\text{g}/\text{mL}^{-1}$ at pulp hydroethanolic extract [25]. <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R
<i>Euterpe oleracea</i> Mart (Açaí)	Areaceae	Pulp	Phenolic compounds: catechin, gallic acid, chlorogenic acid, caffeic acid, [19], cyanidin-3-O-glucoside and cyanidin-3-O-	<i>in vitro</i> : <i>Caenorhabditis elegans</i> after exposed at açai aqueous	<i>in vitro</i> : Pretreatment of β cell with cyanidin-3-O-glucoside (0.5 $\mu\text{mol}/\text{L}$)	<i>in vitro</i> : SH-SY5Y cells culture were protected by açai

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
			<p>rutinoside [18]. Flavonoid: anthocyanin, luteolin, apigenin and chrysin [19, 23].</p>	<p>extract (100 mg/mL) for 48 hours showed scavenging ROS 79.61 ± 3.33 % inhibition [18]. Scavenging ROS (IC₅₀ 31.25 ± 2.31 ppm) at ethanolic extract [98].</p> <p><i>in vivo:</i> <i>Caenorhabditis elegans</i> exposed at açai aqueous extract (100 mg/mL) for 48 hours improved redox status under oxidative stress conditions [18]. Açai pulp intake (200 g/day) in healthy women for 4 weeks reduced the production of ROS [99].</p> <p>Mice pretreated with açai pulp (200 g/kg) for 14 kg showed ability to control the response to oxidative stress induced by 5-FU [100].</p>	<p>prevented cell death induced by H₂O₂ (800 or 1,200 µmol/L) [97].</p> <p><i>in vivo:</i> Açai pulp intake (100 g twice daily) in healthy overweight population for 4 weeks reduced in fasting glucose levels and in total cholesterol [64].</p>	<p>hydroethanolic extract at 5 µg/mL after exposed to rotenone [19]. SH-SY5Y cells culture were protected by açai hydroethanolic extract at 50 µg/mL after exposed to H₂O₂ [77]. PC12 cells culture were protected by açai aqueous extract (0.5 – 50 µg/mL) exposed to β-amyloid protein (0 – 50 µg/mL) for 48 hours [78].</p> <p><i>in vivo:</i> Freeze-dried açai poder intake (2 g/kg) in rats for 7 weeks showed neuromodulatory effects in critical brain regions involved in memory, cognition, and overall brain function</p>

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
						[101]. Mice were treated with acai juice (10 μ L/g b.w. by gavage once a day) for 4 days significantly protects against convulsion PTZ-induced [81].
<i>Eugenia stipitata</i> MacVaugh (Araçá-boi or Araza)	Myrtaceae	Pulp and peel	Phenolic compound: gallic acid [33]. Carotenoid: lutein, α -carotene, β -carotene, cryptoxanthin, zeaxanthin and zeinoxanthin [33].	<i>in vitro</i> : Scavenging ROS (IC ₅₀ 2.65 mg/L) at ethanolic extract [48]. Scavenging ROS (IC ₅₀ 0.69 \pm 0.23 μ g/mL) at ethanolic extract [49]. <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R
<i>Mauritia flexuosa</i> L. f. (Buriti)	Arecaceae	Pulp	Phenolic compound: coumaric acid, ferulic acid, caffeic acid, protocatechuic acid chlorogenic acid and quinic acid [17]. Flavonoids: catechin, epicatechin, apigenin, luteolin, myricetin, kaempferol and quercetin [17]. Carotenoid: α -carotene, β -carotene and lutein [21].	<i>in vitro</i> : Scavenging ROS (IC ₅₀ 704.21 \pm 25.14 μ g/mL) at methanolic extract [102]. <i>in vivo</i> : During 60 days, 10 g (dry pulp) was added to the diet for 100 g total animal weight, there was able to increase the levels of	<i>in vitro</i> : N/R Adipocytes culture were able to active the entire glucose uptake machinery by effectively in some way with insulin receptor after the incubation of protocatechuic acid (25 μ mol/L or 3.85 μ g/mL) [103].	<i>in vitro</i> : N/R <i>in vivo</i> : N/R

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
				NPSH compounds and thereby prevent oxidative stress in male rats [104].	<i>in vivo</i> : N/R	
<i>Myrciaria dubia</i> (HBK) McVaugh (Camu-camu)	Myrtaceae	Pulp	Phenolic compound: ellagic acid [34] [105], catechin, delphinidin 3-glucoside, cyanidin 3-glucoside, rutin [105] and proanthocyanidins [107]. Flavonoids: quercetin, myricetin [105] and catechin [34] [105]. Organic compound: Ascorbic acid [107].	<i>in vitro</i> : The total antioxidant activity of camu-camu was 9.72 of fruit/g of DPPH, with EC ₅₀ 116.71 µg/mL [106]. <i>in vivo</i> : N/R Aqueous camu-camu frozen pulp extract (3 g/kg b.w.) in STZ-diabetic rats for 30 days reduced dyslipidemia bringing total HDL-cholesterol and triglycerides levels to values found in control rats [108].	<i>in vitro</i> : Camu-camu freeze-dried extract showed α-glucosidase inhibition (IC ₅₀ 5.57 ± 1.05 µg/mL of reaction) for Amazonian and (IC ₅₀ 2.98 ± 1.12 µg/mL of reaction) São Paulo samples [61]. <i>in vivo</i> : Camu-camu pulp intake (25 mL pulp juice daily) in obese rats for 12 weeks reduced glucose, cholesterol, triglycerides and insulin levels [8].	<i>in vitro</i> : N/R <i>in vivo</i> : Incubation of aqueous extract (5 mg/mL) for 8 hours in transgenic <i>Caenorhabditis elegans</i> strains showed a significantly reduce the β-amyloid protein aggregation induced paralysis in the Alzheimer's disease model. Also, there was abrogation in neurotoxicity, mainly in dopaminergic neurons affected in Parkinson's disease [82].
<i>Paullinia cupana</i> Kunth (Guarana)	Sapindaceae	fruit	Phenolic compound: epicatechin, catechin [37] and proanthocyanidin [38]. Alkaloid: caffeine [37].	<i>in vitro</i> : Daily intake of 3 g guarana powder containing 90 mg	<i>in vitro</i> : N/R Insoluble-bound polyphenol fraction (IBPP) and soluble	<i>in vitro</i> : Exposition of aqueous extract (1 mg/mL) for 24 hours

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
				catechin and 60 mg epicatechin was able to reduce H ₂ O ₂ induced DNA damage in lymphocytes, as well as promoting an increase in the activities of catalase and glutathione peroxidase at 1 hour post-dose [109]. TRAP: 0.01 – 10 µg.mL ⁻¹ for hydroethanolic guarana extract [110]. Exposition of low-level laser therapy (4 J/cm ²) and hydroethanolic guarana extract (5 µg/mL) for 72 hours significantly decreased protein carbonylation, lipoperoxidation and DNA oxidation in human dermal fibroblastos cells culture with guarana [111]. <i>in vivo</i> : An epidemiological	polyphenol fraction obtention (SPP) of guarana powder showed α-glucosidase inhibition IC ₅₀ 1.624 µg GAE/mL (IBPP) and IC ₅₀ 9.504 µg GAE/mL (SPP) [38]. <i>in vivo</i> : N/R	in SH-SY5Y cells culture promoted the protection against protein glycation and aggregation β-amyloid [37]. <i>in vivo</i> : Multivitamin and mineral complex with guarana (222.2 mg per tablet) consumed 1 hour prior to moderate-intensity exercise can improve cognitive performance up to 90 min post-exercise in humans [83].

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
				study showed a significant association between lower levels of advanced oxidative protein product and habitual guarana consumption by na elderly population residing in the Amazon Riverine region (Brazil) [112].		
<i>Solanum sessiliflorum</i> Dunal (Cubiu)	Solanaceae	Pulp	Coumarins: <i>p</i> -coumaric acid, <i>p</i> -hydroxidihydrocumaric acid [42], vanilic acid and 5-caffeoylquinic acid [43]. Flavonoid: naringenin [42]. Carotenoids: lycopene, α -carotene and β -carotene [43]. Terperne: bisabolol, phenylpropene and apiole [43]. Alkaloid: solasonine [43].	<i>in vitro</i> : N/R Scavenging ROS (IC ₅₀ 606.3 \pm 3.5 μ g/mL) at hydroethanolic extract [113]. <i>in vivo</i> : Intake of cubiu (250, 375 and 500 mg/kg b.w. for 14 days) reduced the lipid peroxidation induced by DXR in liver and heart of rats [39].	<i>in vitro</i> : N/R <i>in vivo</i> : N/R	<i>in vitro</i> : N/R <i>in vivo</i> : N/R
<i>Theobroma grandiflorum</i> (Wild. ex Spreng.) Schum. (Cupuaçu)	Malvaceae	Pulp	Flavonoids: flavan-3-ols, procyanidins, flavones, catechin, and epicatechin [30]. Fatty acids: palmitic acid, stearic acid, oleic acid,	<i>in vitro</i> : Consumption of hydromethanolic cupuaçu extract (7.2 g/kg b.w.) for 40 days reduced lipid	<i>in vitro</i> : N/R <i>in vivo</i> : N/R Hydromethanolic cupuaçu extract (7.2 g/kg b.w.) in STZ-	<i>in vitro</i> : N/R <i>in vivo</i> : N/R

Scientific name (common name)	Botanical family	fruit / part	Chemistry class / Bioactive compound	Antioxidant activity	Hypoglycemic action	Neuroprotective activity
			linoleic acid and α -linoleic acid [31].	peroxidation induced by STZ in rats [31]. Scavenging ROS (DPPH 1913 \pm 228 μ mol TE/100 g DW) at hydromethanolic extract [31]. <i>in vivo</i> : N/R	diabetic rats for 40 days demonstrated positive effects on lipid profile [31].	

Legend: 5-FU: 5-Fluorouracil. DPPH: 2,2-Diphenil-1-picrylhydrazyl. DXR: doxorubicin. DW: dry weight. GAE: gallic acid. NPSH: non-protein sulfhydryl. PHA: phytohemagglutinin. ROS: reactive oxygen species. RNS: reactive nitrogen species. Scavenging ROS or RNS (antioxidant action) by DPPH test. STZ: streptozotocin. TE: Trolox equivalent. TRAP: Total radical-trapping. N/R: not reported

This review shows studies with *in vitro* antioxidant assay based on the reduction of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical in all plant species. Ethanolic *Eugenia stipitata* MacVaugh [48,49] and hydroethanolic *Caryocar villosum* (Aubl.) Pers extracts [6,25] showed the most significant capacity to stabilize radicals at a lower concentration, exhibited half-maximal inhibitory concentration (IC₅₀) 0.69 µg/mL for reactive oxygen species (ROS) and 0.05 µg/mL for reactive nitrogen species (RNS), respectively. Exceeding the antioxidant capacity of methanolic *Malpighia umbellata* Rose fruits extract (20.51 µg/mL) [50] or isolated molecules such as chlorogenic acid (2.1 µg/mL) and caffeic acid (1.44 µg/mL) in methanolic solution [51]. *In vivo* assays provide various information regarding the antioxidant ability like the oil extracted from *Astrocaryum aculeatum* Meyer (500, 1000 and 2000 mg/kg b.w.) [52] showed a significant antioxidant effect in mice exposed to doxorubicin (DXR) and the ingestion of *Solanum sessiliflorum* Dunal pulp (250, 375 and 500 mg/kg b.w. for fourteen days) reduced the lipoperoxidation in rats exposed to DXR [39] demonstrated a critical antioxidant effect concerning the study with *Mimosa pudica* L. (400 mg/kg b.w.) [53], *Centella asiatica* (L.) Urb. (500 mg/kg b.w.) [54] and *Taraxacum officinale* (L.) Weber ex F.H. Wigg (500 mg/kg/day) [55] in model animals against oxidative stress damage.

Glycemic control remains a delicate balancing act in animals, mainly in humans. The diabetic patient is responsible for maintaining euglycemic blood glucose levels, a goal requiring education, decision strategies, and the wisdom to avoid hyper- and hypoglycemia that could be lethal [56]. In diabetic patients, the persistent homeostatic glucose mismatch promotes a variety of secondary complications, including cardiovascular diseases [57], retinopathy, and associated blindness, neuropathies that can cause amputations and kidney diseases [58]. Besides, studies showed neurodegeneration and cognitive decline in insulin-resistant patients who do not show hyperglycemia (pre-diabetes), concluding that hyperglycemia as crucial as the loss of insulin action [59].

Recently, α-glucosidase inhibition in the modulation of carbohydrate digestion has been investigated, thereby delaying postprandial glycemia, which is an efficient way to control the early stages of type 2 diabetes. *In vitro* studies

were predominant with α-glucosidase inhibitors as *Astrocaryum aculeatum* Meyer native fruits and commercial frozen pulps, which presented IC₅₀ 1.7 mg of sample dw/mL of reaction [60], *Myrciaria dubia* (HBK) McVaugh freeze-dried extract exhibited IC₅₀ 5.57 µg/mL of reaction [61], and *Paullinia cupana* Kunth demonstrated soluble polyphenol fraction IC₅₀ 9.504 µg GAE/mL [38] a stronger inhibitory potency than acarbose IC₅₀ 250.49 µg/mL [62] or hydroethanolic *Eugenia uniflora* L. extracts IC₅₀ 66.3 µg/mL [63]. *In vivo* tests to verify the hypoglycemic effect, *Euterpe oleracea* Mart pulp intake (100 g twice daily for four weeks) in a healthy overweight population [64] and *Myrciaria dubia* (HBK) McVaugh pulp intake (25 mL pulp juice daily for twelve weeks) in obese rats reduced glucose levels demonstrated necessary therapeutic actions [8]. However, lower proportions (dose per period) compared with studies in *Silybum marianum* (L.) Gaertn (140 mg three times daily for forty-five days) [65], *Capparis spinosa* L. fruit extract (1200 mg daily for two months) [66], *Zingiber officinale* Roscoe powder (3000 mg daily for three months) [67] or *Berberis vulgaris* L. (200 mL juice daily for eight weeks) [68] which improved the glycemic indices in patients with type 2 diabetes. Also, hydromethanolic *Theobroma grandiflorum* (Wild. ex Spreng.) Schum. extract (7.2 g/kg b.w. for forty days) demonstrated positive effects on lipid profile in streptozotocin-diabetic rats [31]. Still, reduced hypoglycemic activity compared to leaves' extract of *Bauhinia variegata* (L.) Benth (0.2 and 0.4 g/kg for seven days) or metformin (0.5 g/kg for seven days) [69].

Neuroprotection is a widely studied treatment option for central nervous system disorders, as neurodegenerative diseases. The essential pathological mechanisms in brain damage are inflammatory reaction, blood-brain barrier disruption, oxidative stress, and neuronal apoptosis [70,71,72,73]. Studies suggest the therapeutic effects of various natural antioxidants against cerebral damage [74,75,76].

In vitro studies with hydroethanolic *Euterpe oleracea* Mart extract at 5 and 50 µg/mL protected SH-SY5Y and PC12 cells culture when verifying the neuroprotective action after exposure to rotenone, H₂O₂ and β-amyloid aggregation [19,77,78]. Also, aqueous *Paullinia cupana* Kunth extracts at 1 mg/mL promoted SH-SY5Y cells culture protection in front of protein glycation and aggregation β-amyloid [37].

Demonstrating significant therapeutic effect but at higher concentrations compared to Razadyne® (2.873 µg/mL) [79] used mainly in the treatment of Alzheimer's disease or [6]-gingerol (2.94 µg/mL for 24 hours), a phenol compound found in fresh ginger (*Zingiber officinale* Roscoe) protected against β-amyloid cytotoxicity, apoptotic cell death and DNA fragmentation in SH-SY5Y cells [80]. Besides *in vivo* studies, *Euterpe oleracea* Mart juice (10 µL/g b.w. for four days) significantly protects mice against convulsion pentylenetetrazol-induced [81]. Aqueous *Myrciaria dubia* (HBK) McVaugh extract (5 mg/mL for eight hours) reduced β-amyloid aggregation and neurotoxicity in dopaminergic neurons in *Caenorhabditis elegans* [82]. Ingestion of multivitamin and mineral complex with *Paullinia cupana* Kunth (222.2 mg per tablet) 1 hour before moderate-intensity exercise can improve cognitive performance in humans [83] compared to drugs used to treat Alzheimer's (Rivastigmine, 12 mg three times/day) [84], Parkinson's (Levodopa, 25 – 100 mg three times/day) [85] or hydroethanolic *Caryocar brasiliense* A.St.-Hil extract (300 mg/kg b.w.) as cholinesterase inhibitor in rats [26] suggests a better therapeutic effect.

This review showed extracts of native fruits of the Amazon region, which demonstrated important antioxidant, hypoglycemic and neuroprotective actions based on *in vitro* and *in vivo* assays. It is possible to associate Amazonian fruits' consumption with nutritional value and a potential nutraceutical in this context.

4. MATERIALS AND METHODS

Studies related to the presence of compounds with antioxidant, hypoglycemic, and neuroprotective activities of extracts from ten native fruits to the Amazon region (described in the period from 2010 to 2020) were identified by searching electronic databases such as Pubmed, Scielo, ScienceDirect, and Web of Science including publications in English, Spanish, and Portuguese. The studies eligible for this review included trials carried out on humans, animal models, or cell culture submitted to oxidative stress or effects induced by molecules involved in the etiology in metabolic disease,

characterized by high blood glucose levels (hyperglycemia) and neurodegeneration.

The terms used as an inclusion criterion were "Amazonian fruits," "Scientific name of the plant," as well as the biological effects "antioxidant," "hypoglycemic," and "neuroprotective" extracts from *Astrocaryum aculeatum* Meyer, *Bactris gasipaes* Kunth, *Caryocar villosum* (Aubl.) Pers, *Euterpe oleracea* Mart, *Eugenia stipitata* MacVaugh, *Mauritia flexuosa* L. f., *Myrciaria dubia* (HBK) McVaugh, *Paullinia cupana* Kunth, *Solanum sessiliflorum* Dunal, and *Theobroma grandiflorum* (Wild. ex Spreng.) Schum. However, excluded studies involving leaves, roots, flowers, stem extracts, and documents with preliminary information related to technological processing and functional effects of extracts Amazonian plants missing. In this review, we reached out to 801 publications, of which 64 papers were selected (Fig. 1). After searching on the database, the family Arecaceae which represented by four different plant species (*Astrocaryum aculeatum* Meyer, *Bactris gasipaes* Kunth, *Euterpe oleracea* Mart, and *Mauritia flexuosa* L. f.), followed by the family Myrtaceae (*Eugenia stipitata* MacVaugh and *Myrciaria dubia* (HBK) McVaugh) with two representatives while the families Caryocaraceae (*Caryocar villosum* (Aubl.) Pers), Sapindaceae (*Paullinia cupana* Kunth), Solanaceae (*Solanum sessiliflorum* Dunal) and Malvaceae (*Theobroma grandiflorum* (Wild. ex Spreng.) Schum.) had one plant species representative each one.

Among the biological effects selected, studies showed antioxidant activity in all plant species. In contrast, the families Arecaceae (*Bactris gasipaes* Kunth), Caryocaraceae, Myrtaceae (*Eugenia stipitata* MacVaugh), and Solanaceae were ineffective to glycemic control. No studies with fruit extract and neuroprotective action founded using the families Arecaceae (*Astrocaryum aculeatum* Meyer, *Bactris gasipaes* Kunth, and *Mauritia flexuosa* L. f.), Caryocaraceae, Myrtaceae (*Eugenia stipitata* MacVaugh), Solanaceae, and Malvaceae. Hence, the families Arecaceae (*Euterpe oleracea* Mart), Myrtaceae (*Myrciaria dubia* (HBK) McVaugh), and Sapindaceae (*Paullinia cupana* Kunth) (Fig. 2) presented significant studies with bioactive antioxidant compounds, hypoglycemic and neuroprotective, as shown in Table 1.

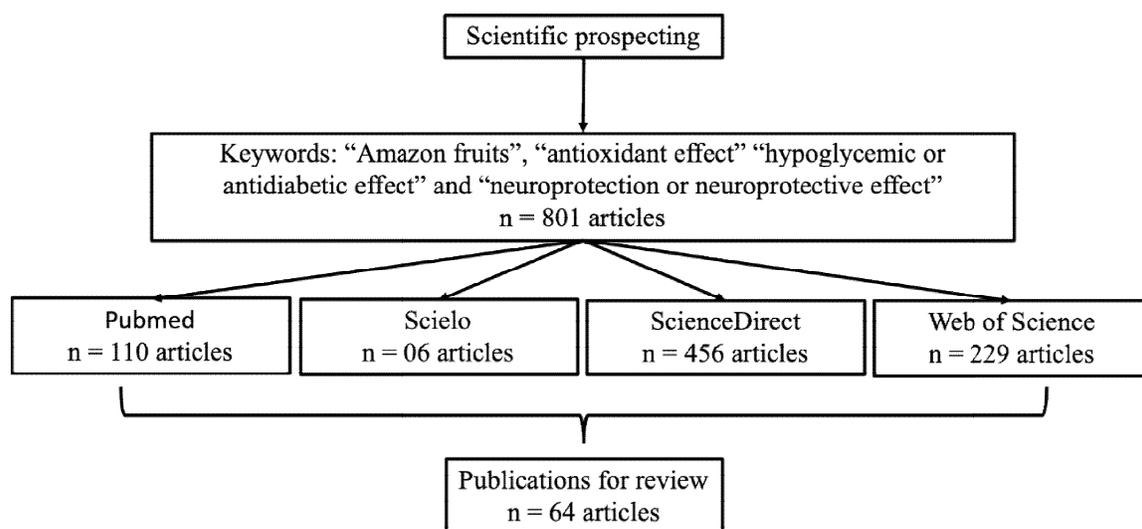


Fig. 1. Selection of studies related to the presence of compounds with antioxidant, hypoglycemic, and neuroprotective activities of extracts from ten native fruits to the Amazon region

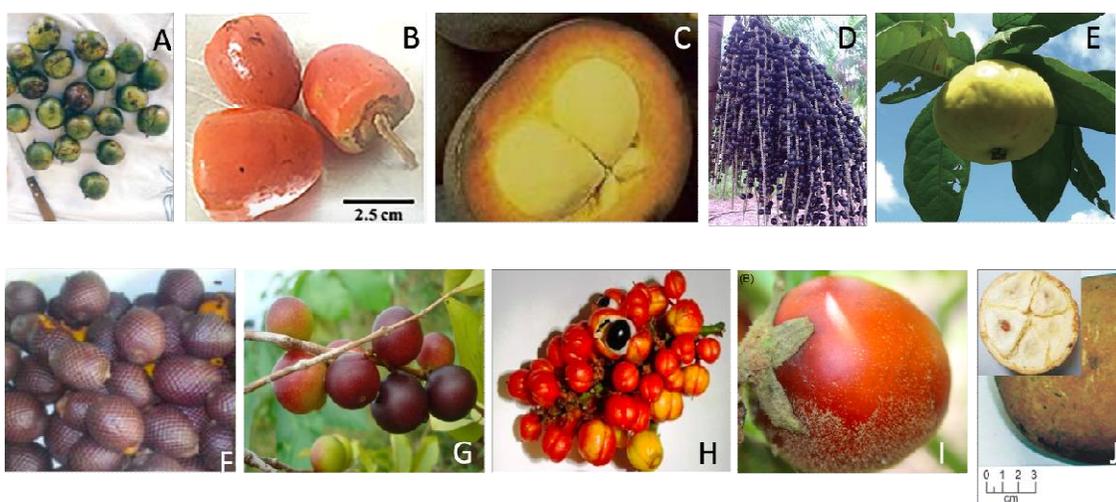


Fig. 2. General vision of the fruits native of Amazon region

Legend: A = *Astrocaryum aculeatum* Meyer [86]; B = *Bactris gasipaes* Kunth [87]; C = *Caryocar villosum* (Aubl.) Pers [88]; D = *Euterpe oleracea* Mart [89]; E = *Eugenia stipitata* MacVaugh [90]; F = *Mauritia flexuosa* L. f. [91]; G = *Myrciaria dubia* (HBK) McVaugh [92]; H = *Paullinia cupana* Kunth [93]; I = *Solanum sessiliflorum* Dunal [94]; and J = *Theobroma grandiflorum* (Wild. ex Spreng.) Schum. [95]

5. CONCLUSION

This review provides an overview of native fruits to the Amazon region usually consumed by the local population or processed and marketed as a functional food. Recent studies with extracts of the species described here have shown significant antioxidants in all plant species. However, in the families, Arecaceae

(*Astrocaryum aculeatum* Meyer, *Bactris gasipaes* Kunth, and *Mauritia flexuosa* L. f.), Caryocaraceae, Myrtaceae (*Eugenia stipitata* MacVaugh), Solanaceae, and Malvaceae showed only neuroprotective activities. However, the families Arecaceae (*Euterpe oleracea* Mart), Myrtaceae (*Myrciaria dubia* (HBK) McVaugh), and Sapindaceae (*Paullinia cupana* Kunth) presented significant studies with bioactive

antioxidant compounds, hypoglycemic and neuroprotective. Therefore, new research should be conducted considering the enormous potential in the mechanisms to protect against oxidative stress, hyperglycemia, or neuronal degeneration or even potentially delay and prevent associated pathologies through the consumption of fruits native to the Amazon region.

ACKNOWLEDGEMENTS

The authors are grateful to the UFAM (Federal University of Amazonas) and also thank two anonymous reviewers for their support through constructive critics and corrections on this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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