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Review Article

Euterpe oleraceae (Açaí), *Bixa orellana* (Annatto), and *Myrciaria dubia* (Camu-camu): A Review of Preclinical Evidence of Anti-senescence Potential

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ABSTRACT
Aging is a complex process resulting from internal and external changes, culminating in a decreased efficacy of cognitive and other biological functions. Studies report that oxidative stress, immunosenescence, inflammaging, and cell senescence are involved in aging. Continuous research is performed seeking treatments delaying such processes to achieve healthy aging, including nutrition and nutraceuticals. In this article, we review the potential of some plants from the Amazon rainforest that have been gaining attention in healthspan, namely *Euterpe oleraceae* (Açaí), *Myrciaria dubia* (Camu-camu), and *Bixa orellana* (Annatto).

Keywords: Aging, Cell senescence, *Euterpe oleracea*, *Myciaria dubia*, *Bixa orellana*.

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INTRODUCTION

Aging is a complex multifactorial process that causes a gradual decline in normal physiological functions and can be influenced by genetics, environment, lifestyle, exercise, and nutrition.[1] This body decline is a risk factor for Age-Related Diseases (ARD), including infectious, inflammatory, neurodegenerative diseases, diabetes, osteoarthritis, and cancer.[2] According to the world population data from the World Health Organization, the population of 60 years and above is increasing annually, and it is estimated that by 2050 this elderly population will reach 2.1 billion.[3]

Phenotypically, aging causes the accumulation of senescent cells, increased oxidative stress, mitochondrial dysfunction, increased inflammatory state a process called "inflammaging", genomic instability, stem-cell exhaustion, and epigenetic alterations, among other factors that will contribute to ARDs.[4-6]

In order to improve the human quality of life during its lifespan, a new concept emerged in research called healthspan, which seeks better health, well-being, and higher life expectancy in the elderly population.[7,8] The literature shows some plant-derived compounds with beneficial effects in this aspect, potentially promoting healthy aging in humans.[9] This approach could have a better impact by treating a common underlying factor–such as cell senescence, inflammaging, and increased oxidative stress, among others than treating the ARDs individually.

This paper aims to review some plants species and their main compounds–found in the Amazonian Rainforest that show promising potential in promoting healthspan: *Euterpe oleraceae* (Açaí), *Myrciaria dubia* (Camu-Camu), and *Bixa orellana* (Urucum, Annatto).

Cell senescence and aging

Approximately 60 years ago, Leonard Hayflick and Paul Moorhead made a significant observation that cells possess a finite ability to multiply, leading to the formulation of the cell senescence hypothesis.[10] Nowadays, it is widely accepted that cell senescence represents a phase in which cells gradually lose their ability to replicate, ultimately resulting in the complete cessation of the cell cycle.[2,11] Cell senescence serves an adaptive function within the organism, as it hinders tumor growth while promoting wound healing and tissue repair.[12,13] However, the accumulation of senescent cells over an individual's lifespan contributes to age-related diseases, as we will delve into further discussion.

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The process of senescence can manifest as either acute or chronic. Acute senescence is a programmed phenomenon characterized by short-lived cells that serve beneficial purposes, exhibit rapid kinetics, and contribute to tissue maintenance. Conversely, chronic senescence is a long-term process resulting from unscheduled damage, forming long-lived and detrimental senescent cells. Such cells are associated with harmful processes, including tissue dysfunction and tumorigenesis. There is a third type of senescence, known as embryonic senescence, which occurs during development.[6,14] However, in this review, our focus will be solely on senescence processes in adults, emphasizing chronic senescence due to its relevance in Age-Related Diseases (ARDs).

The mechanisms underlying cell senescence are intricate and not fully comprehended, although it is recognized that it can transpire through two distinct pathways: non-replicative stress-induced premature senescence (SIPS) and telomere-dependent replicative senescence.[11,15] Non-replicative senescence via SIPS occurs when cells experience cumulative insults, which can originate from intrinsic factors such as oxidative stress, mitochondrial dysfunction, heightened activation of oncogenes, and endoplasmic reticulum stress, or extrinsic factors like exposure to physical and chemical genotoxic stimuli. These insults can lead to DNA damage.[16]

Telomere-dependent replicative senescence occurs due to telomere shortening.[17] Telomeres are structures consisting of repetitive nucleotide sequences found at the ends of chromosomes, playing a crucial role in their maintenance by safeguarding them against fusion and degradation.[18,19] As cells divide, a terminal portion of the chromosome fails to replicate, leading to the gradual erosion of telomeres by around 50 to 200 base pairs in the replicated DNA (Figure 1). This progressive telomere shortening eventually exposes an uncapped double-stranded chromosome end, which the cell recognizes as a double-strand break (DNA damage).[14,19,20]

Regardless of whether DNA damage is caused by SIPS or telomere shortening, it triggers DNA Repair Responses (DRRs). The Mre11/Rad50/NBS1 (MRN) complex detects DNA errors and recruits a cascade of serine/threonine-nonspecific kinases, ATM (Ataxia-Telangiectasia Mutated), and ATR (ATM and Rad3-related). ATM and ATR, in turn, recruit CHK2 and CHK1, respectively, leading to phosphorylation of p53 and subsequent activation of p21CIP1 (Figure 2).[21] P21 inhibits Cyclin-dependent kinase (CDK) 2, resulting in hypophosphorylation of the Retinoblastoma Protein (RB), activating it, and causing a reversible cell cycle exit.[14]

Up to this point, the cell cycle arrest is still reversible, and the cell can repair DNA damage in this state, known as early senescence. However, if DRRs persist, they activate the INK4/ARF locus. Typically, this locus is silenced by Polycomb Repressive Complexes (PRC), but when activated, it encodes factors such as p16INK4a and ARF. P16INK4a can inhibit CDK4 and CDK6, leading to hypophosphorylation of RB and subsequent activation. Additionally, ARF can activate p53 by inhibiting MDM2 (mouse double minute). Unlike p53 activation alone, the activation of p16INK4a causes a stable and irreversible cell cycle arrest known as full senescence.[6,14]

Cell cycle arrest is a key characteristic of senescent cells, effectively halting the propagation of DNA damage. Senescent cells differ from quiescent cells in that they no longer respond to growth and mitogenic factors. Moreover, they are distinct from terminally differentiated cells, as the latter cease replication due to a predetermined developmental program rather than stress-induced mechanisms.[14] Senescent cells exhibit discernible phenotypic alterations, including enlarged size, flattened and irregular shape, larger nuclei, prominent nucleoli, increased cytoplasmic vacuolization, elevated protein levels, augmented Golgi complex, and the formation of distinctive senescence-associated heterochromatin foci.[11,18,21]

A widely used marker for identifying senescent cells is Senescence-associated beta-galactosidase (SA-β-gal). Typically, SA-β-gal can be detected in non-senescent cells at a pH of 4-4.5. However, in senescent cells, the lysosomal content and activity increase, allowing this marker to be detected at a higher pH of 6.0 using di-D-galactopyranoside in flow cytometry analysis.[13,14,20,22] It is important, however, to employ other markers in combination, such as p16 and p21, for a comprehensive characterization of senescent cells.[11]

Even though full senescent cells cease to divide, their metabolism remains active. As a result, they can impact their surrounding environment by releasing chemokines, extracellular matrix-degrading enzymes, and inflammatory cytokines, in a phenomenon known as the Senescence-Associated Secretory Phenotype (SASP).[10,23,24] SASP is regulated through various pathways, including Nuclear-Factor κB (NF-κB) and the mammalian Target of Rapamycin (mTOR).[13] SASP not only has detrimental effects and contributes to the pathogenesis of Age-Related Diseases (ARDs), but it can also have a paracrine

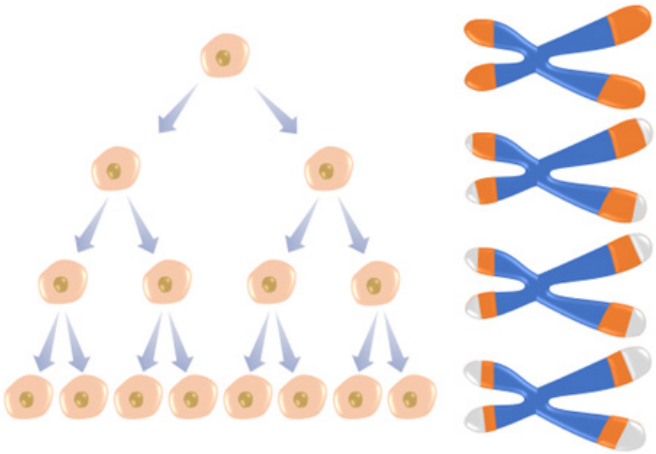


Figure 1: Telomeres shorten as the cells divide.

effect on nearby cells, inducing them to undergo senescence.[11] Alongside cell cycle arrest, SASP represents the second hallmark feature of full senescent cells.

BOTANICAL DESCRIPTION

Euterpe oleraceae Mart

Euterpe oleracea, a tropical palm tree belonging to the Arecaceae family, is renowned for its fruits known as "Açaí".[25] This species is native to South America and primarily found in floodplain areas and along the Amazon River, particularly in northern Brazil, the Guianas, and Venezuela.[26] Brazil is the largest producer, consumer, and exporter of Açaí worldwide.[27] According to the Brazilian Institute of Geography and Statistics (IBGE), the fruit's production surpassed 222 tons in 2019. Açaí is considered a "superfruit" due to its high antioxidant and therapeutic potential, and it is gaining popularity in other countries, including the USA, Japan, China, and Europe.[28]

Euterpe oleracea is a multistemmed palm with clumps containing up to 25 stems. Each stem can grow to a height of 3 to 20 m and has a diameter of 7 to 18 cm in mature specimens. At the top of each stem, there are between 8 and 14 compound pinnate leaves arranged spirally, with each leaf having 40 to 80 pairs of leaflets. The inflorescences develop below the leaves, shielded from direct sunlight. In the first two-thirds of the raquilas (flower-bearing stems), the flowers are arranged in triads, consisting of a female flower flanked by two male flowers. In the final third of the raquilas, only male flowers are present.[29] The fruit is spherical, with a diameter of 10 to 12 mm, a smooth texture, and a deep purple color when fully mature (around 175 days).[30] The seeds, which comprise 90% of the fruit's diameter and weight, are light brown.[31]

This species is rich in essential macro and micronutrients, including phosphorus, zinc, iron, manganese, copper, boron, chromium, calcium, magnesium, potassium, and nickel. The fruit's dry weight comprises lipids (50%), fibers (25%), and

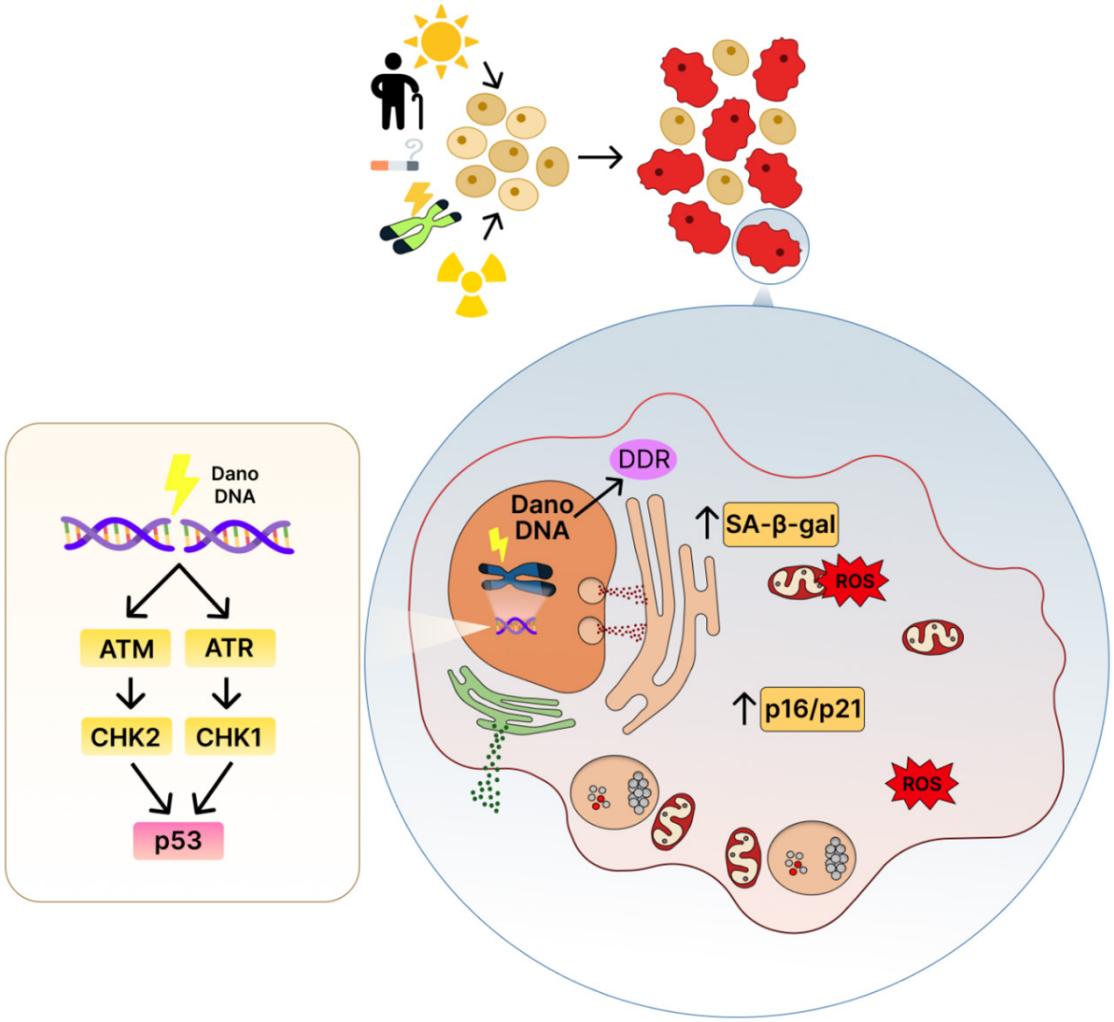
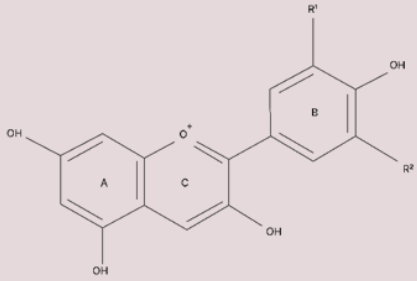
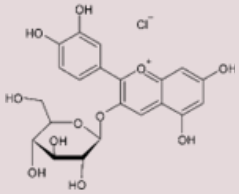
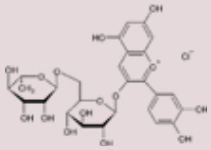
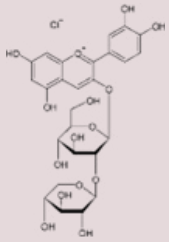
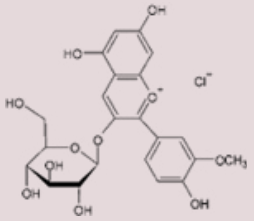
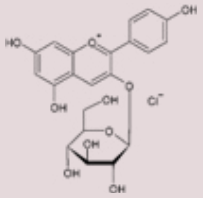
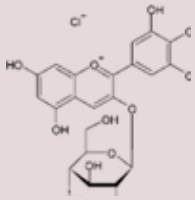
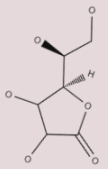
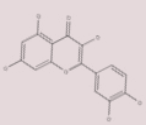
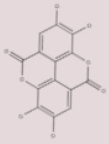
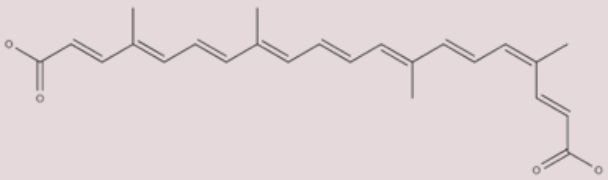
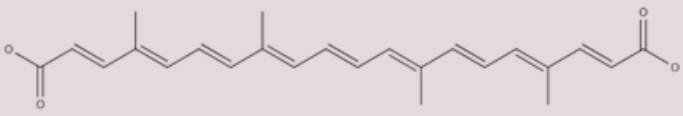
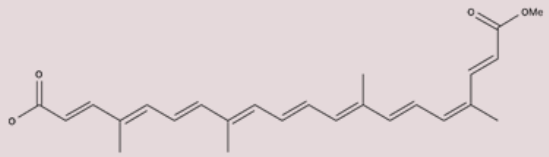
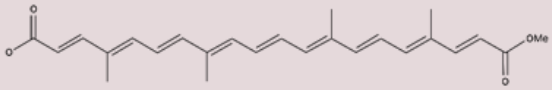
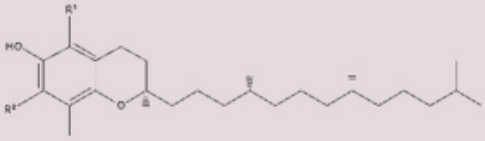
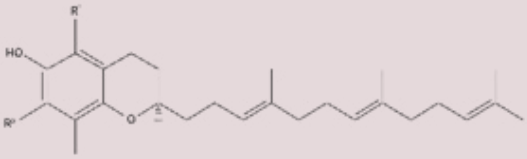
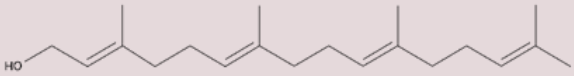


Figure 2: This schematic diagram describes the cell senescence development. The overproduction of ROS and other stresses can damage macromolecules, including the DNA, triggering DNA damage response (DDR). Age-induced telomeres shortening also can cause DDR. The increased DDRs lead to the activation of p16 and p21; also, DNA damage can be detected by the MRN complex triggering a cascade that activates p53; the activation of p16, p21, p53 will cause cell cycle arrest. Eventually, the senescent cells became SASP, contributing to ARDs.

Table 1: Phytochemicals and their Molecular Structures in Amazonian Plant Species.

Plant species				
Euterpe oleraceae Mart.	Basic structure of anthocyanins			
	Main anthocyanins found in *Euterpe oleraceae* Mart.			
		Cianidina-3-O-glucosídeo	Cianidina-3-O-rutenosídeo	Cianidina-3-O-sambubiosídeo
				
		Peonidina-3-O-rutenosídeo	Pelargonidina-3-O-glucosídeo	Delfinidina-3-O- glucoside
Myrciaria dubia	Bioactive compounds found in *Myrciaria dubia*			
		Ascorbic acid	Quercetin	Ellagic acid
Bixa Orellana	Caroteinoids found in *B. orellana*			
		Cis-norbixin		
				

Plant species				
		Trans-norbixin		
				
		Cis-bixin		
				
		Trans-bixin		
	Tocopherols and Tocotrienols			
		Tocopherol		
				
		Tocotrienol		
				
		Geranylgeraniol		

proteins (10%).[30] Açaí is a source of unsaturated fatty acids, including omega-6 and omega-9, as well as Vitamins A, C, D, and E.[32]

In addition to its nutritional value, açaí contains a significant amount of bioactive compounds, including flavonoids and phenolic compounds such as protocatechuic acid, epicatechin, benzoic acid, caffeic acid, chlorogenic acid, ferulic acid, syringic acid, vanillic acid, p-coumaric acid, orientin, isoorientin, vitexin, and procyanidins.[33] Among these compounds, anthocyanins are particularly noteworthy and are responsible for the red, blue, or purple pigmentation in fruits and vegetables.[34]

The specific anthocyanins found in açaí are depicted in Table 1, with the most abundant ones being cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside.[29,35] These compounds play a crucial role in the vibrant colors exhibited by açaí. It is worth noting that the prevalence of cyanidin-3-O-rutinoside increases during the late stages of fruit maturation, indicating that the chemical composition of the fruit is influenced by its maturation process.

Euterpe oleraceae against aging

In a study by Peixoto *et al.* a hydroethanolic extract of *E. precatoria*, a species of "Açaí" with a similar composition to *E. oleraceae*, was tested for its effects on oxidative stress and longevity in the nematode *Caenorhabditis elegans*. The major anthocyanin identified in the extract was cyanidin-3-rutinoside, representing 89% of the total anthocyanin content at a concentration of 0.5 μg/mg. The researchers made several interesting observations: 1. The extract significantly increased the survival rate of nematodes exposed to a lethal concentration of juglone in a concentration-dependent manner; 2. The extract decreased the formation of reactive oxygen species caused by juglone in a concentration-dependent manner, indicating its antioxidant activity. This effect was not solely due to free radical scavenging

but also involved modulation of the stress response evidenced by decreased levels of heat shock protein (*hsp-16.2*) and increased levels of superoxide dismutase (*sod-3*); 3. The treatment increased the translocation of DAF-16 from the cytoplasm to the nucleus, allowing the expression of genes involved in stress response, metabolism, and longevity. Mutant nematodes lacking DAF-16 did not exhibit increased survival rates under juglone-induced stress, indicating that the increased stress resistance depended on the DAF-16 pathway; 4. Although the extract did not increase the lifespan of nematodes without juglone-induced stress, it did decrease certain age-related phenotypes, such as muscular decline and pigment deposition; 5. The extract did not cause any significant changes in developmental or fertility parameters.[36]

In another study by Sun *et al.* using *Drosophila melanogaster* (fruit flies), the effect of açaí pulp supplementation was tested *in vivo*, comparing a standard diet and a high-fat diet. The researchers made the following observations: 1. Açaí pulp supplementation (0.5% to 2%) increased the lifespan of female fruit flies fed a high-fat diet by up to 22%. However, no significant lifespan extension was observed in males, possibly due to sex-specific dietary requirements; 2. In female fruit flies receiving a high-fat diet and açaí pulp supplementation, increased transcription of *l(2)efl* (a heat shock protein), *GstD1*, and *MtnA* (detox genes) was observed. Additionally, the expression of *Pepck*, a key enzyme involved in gluconeogenesis, was decreased; 3. Açaí pulp supplementation increased the lifespan of female fruit flies under oxidative stress induced by *sod-1* RNAi, suggesting an enhanced stress resistance.[37] A similar observation was reported by Liedo *et al.*, where supplementation with açaí pulp increased the lifespan of male and female mexflies (*Anastrepha ludens*) receiving a high-sugar diet with 2% fat (palmitic acid).[38] However, no significant changes were observed in flies fed typical diets with yeast extracts.

The study by De Bonomo *et al.* supports the findings of Peixoto *et al.* and Sun *et al.* regarding the increased survival and resistance to oxidative stress with açaí extract treatment in *C. elegans*.[36,37,39] De Bonomo *et al.* observed that treatment with açaí extracts increased the lifespan of *C. elegans* under oxidative and osmotic stress conditions without affecting development or fertility. The treatment was found to decrease sulfhydryl production, activate *gcs-1*, reduce polyglutamine protein aggregation, and decrease proteasome activity. The increased resistance to oxidative stress was dependent on DAF-16 (FoxO) translocation to the nucleus and involved direct radical scavenging. The resistance to osmotic stress was dependent on the OSR-1/UNC-43/SEK-1 pathway. Notably, De Bonomo *et al.* also demonstrated that açaí extract treatment increased oxidative resistance in human umbilical vein endothelial cells *in vitro*. The extract in their study contained 31 mg/100g of total monomeric anthocyanins, with 8.8 mg/100g of Cyanidin 3-O-glucoside and 8.7 mg/100g of Cyanidin 3-O-rutinoside.[39]

In the study by Souza-Monteiro *et al.* using Swiss mice, the authors investigated the effects of açaí juice on Lipopolysaccharide (LPS)-induced depressive-like behavior. LPS treatment is known to induce depressive-like behavior in animal models. The authors found that animals treated with açaí juice exhibited decreased depressive-like behavior, similar to the effect of imipramine, an antidepressant drug. The açaí-treated animals also showed a reversal of increased lipid peroxidation, neurodegeneration, and nitrite levels in the hippocampus. Notably, the mice that received açaí juice had increased mRNA expression for Telomerase Reverse Transcriptase (TERT), an enzyme that maintains telomeres and prevents replicative senescence.[40]

Clinical trials investigating the effects of *Euterpe oleracea* (açaí) have provided promising results. De Liz *et al.* conducted a 4-week randomized crossover study in healthy adults and found that açaí consumption improved HDL (high-density lipoprotein) levels. The study also demonstrated that açaí increased antioxidant defense, as evidenced by increased total antioxidant capacity, catalase and glutathione peroxidase levels, and decreased oxidative stress index. These findings align with preclinical data suggesting the antioxidant properties of açaí.[41]

Aranha *et al.* investigated the effects of *E. oleraceae* in overweight individuals with dyslipidemia who were following a hypoenergetic diet. The group receiving *E. oleraceae* showed reduced levels of 8-isoprostane, a biomarker of oxidative stress, compared to the group following the hypoenergetic diet without açaí. Additionally, unlike the placebo group, the *E. oleraceae* group exhibited decreased levels of IL-6, a pro-inflammatory cytokine. These results indicate that *E. oleraceae* supplementation may have beneficial effects on oxidative stress and inflammation in individuals with dyslipidemia.[42]

In a pharmacokinetic study by Mertens-Talcott *et al.* healthy volunteers consumed açaí anthocyanins, and the authors detected the presence of anthocyanins in human plasma, with peak concentrations observed approximately 2 hr after consumption. Notably, the study revealed that the açaí pulp had a much higher anthocyanin content than the juice.[43] This finding highlights the importance of considering the form in which açaí is consumed when assessing its potential health benefits. The potential of anthocyanins, the major phenolic compounds in açaí, against senescence has been the subject of increasing attention. Chen *et al.* provide a dedicated review on this topic, exploring the role of anthocyanins in mitigating senescence-related processes.[44]

Myrciaria dubia (Kunth) Mc Vaugh (Camu-camu)

M. dubia, commonly known as Camu-Camu, is a tropical plant native to the Amazonian region. It belongs to the Myrtaceae family and thrives in flooded areas such as riverbanks, streams, swamps, and lakes across countries like Brazil, Venezuela, Peru, and Colombia.[45,46] Although the fruit of Camu-Camu has high acidity levels, which can make it challenging to consume directly,

it is widely used in various processed forms such as pulp, juices, beverages, creams, and yogurts.

Camu-Camu is often called a "superfruit" due to its exceptional levels of ascorbic acid (Vitamin C) and phenolic compounds. It is commonly utilized as a supplement in powdered form for the production of sodas, juices, jams, ice creams, nectars, isotonic drinks, and other products.[32,47,48] The fruit's nutritional, technological, and nutraceutical potential has gained attention in local and international markets.[49-51]

Due to its high Vitamin C content, Camu-Camu has garnered interest for its potential health benefits. Vitamin C is an essential nutrient with antioxidant properties that can support the immune system, promote collagen synthesis, and act as a scavenger of free radicals. Additionally, the phenolic compounds present in Camu-Camu contribute to its antioxidant capacity, further enhancing its potential health-promoting effects.[49]

The plant is a shrub reaching between 1.5 and 4 m tall. The leaves are petiolated, simple, and elliptical. Its inflorescences are axially grouped into two pairs.[32] The fruit *M. dubia* is rounded, with 2.5 cm in diameter, red or purple, with a pink mesocarp around four seeds representing 40% of the fruit.[32,50] The species propagation occurs sexually through the seeds but can also occur asexually.[52] The fruits are harvested between March and September, with 50% - 70% of their maturation.[48]

Nutritionally, the fruit is a source of Vitamins (mainly C); minerals such as sodium, potassium, calcium, zinc, magnesium, manganese, and copper; amino acids including serine, valine, leucine, glutamate, 4-aminobutanoate, proline, phenylalanine, threonine, and alanine; and fatty acids like stearic acid, linoleic acid, oleic acid, γ and α linolenic acid, tricosanoic acid and eicosadienoic acid.[49]

Camu-Camu is a shrub that typically grows between 1.5 and 4 m tall. It has petiolated, simple leaves that are elliptical in shape. The plant produces inflorescences arranged in pairs along the axils of the leaves.[32] The fruit is rounded and measures about 2.5 cm in diameter. It can be either red or purple, with a pink mesocarp surrounding four seeds that makeup approximately 40% of the fruit.[32,50] The species primarily reproduces sexually through seeds but can also propagate asexually.[46] The fruits are typically harvested between March and September, at approximately 50% to 70% of their maturation stage.[48]

In terms of nutritional composition, Camu-Camu fruit is a rich source of Vitamins, particularly Vitamin C. It also contains various minerals such as sodium, potassium, calcium, zinc, magnesium, manganese, and copper. The fruit provides several amino acids, including serine, valine, leucine, glutamate, 4-aminobutanoate, proline, phenylalanine, threonine, and alanine. Additionally, Camu-Camu fruit contains fatty acids such as stearic acid, linoleic acid, oleic acid, γ and α linolenic acid, tricosanoic acid, and eicosadienoic acid.[49]

The composition of secondary and bioactive metabolites varies according to its maturation stage and environment.[45] However, in general, there is plenty of compounds with antioxidant capacity, including ascorbic acid, polyphenols like quercetin (42 mg/100 g, dry weight), kaempferol (2 mg/100 g), cyanidin (306 mg/100), ellagic acid (16 mg/100 g), anthocyanins (10 mg/100 g), other phenolic compounds (861 mg/100 g), and flavonoids (6.5 mg/100 g).[32,48,50]

Myrciaria dubia against aging

Besides the high content of ascorbic acid (Vitamin C) and the high antioxidant capacity of its compounds, several biological activities are currently being assessed in *M. dubia* through preclinical studies, including anti-hyperglycemic, anti-hyperlipidemic, antihypertensive, anti-inflammatory, and neuroprotective. All of these activities are related to ARDs; moreover, the polyphenols found in the fruit are reported to modulate cell senescence.[53-56]

Azevêdo *et al.* conducted a study using a low molecular weight fraction of *M. dubia* and demonstrated an increase in the lifespan of *C. elegans* by up to 20%. The treatment led to the upregulation of *sod-3* (3x), sod-4, *clt-1+2+3*, and *skn-1* (the *C. elegans* orthologue of mammalian *Nrf2*), while *gst-4* was downregulated. Interestingly, the treatment also decreased *daf-16*, which was unexpected considering that the lifespan of the animals and *sod-3* expression increased significantly. The authors further investigated the effects of the fraction in an Alzheimer's disease model induced by $A\beta_{1-42}$ aggregation and neurodegeneration induced by MPP+. The treatment showed the potential to prevent both conditions, resulting in 21% less paralysis and up to 21% less neurodegeneration.[53]

Fujita *et al.* conducted a study to assess the inhibition potential of carbohydrate-degrading enzymes by *M. dubia* extracts from two different origins. The authors found that the extracts exhibited low α-amylase inhibitory potential but demonstrated good α-glucosidase inhibitory activity. This suggests that *M. dubia* may have the capacity to inhibit the breakdown and absorption of complex carbohydrates, which could contribute to its hypoglycemic effects. Interestingly, the study also investigated the potential regenerative effects of *M. dubia* pulp by examining its impact on planaria (*Dugesia tigrina*), a type of flatworm known for its regenerative capabilities. The authors reported that treatment with the pulp of *M. dubia* increased the regeneration capacity of planaria compared to untreated animals. This observation suggests that *M. dubia* may possess cellular rejuvenation potential or support the regenerative processes in organisms.[54]

The studies conducted by Surco-Laos *et al.* and Kampkötter *et al.* provide further evidence supporting the potential use of *M. dubia* and its constituent quercetin against aging-related processes.[57,58]

Surco-Laos *et al.* investigated the effects of quercetin and its methylated metabolites, isorhamnetin and tamarixetin, on the longevity of *C. elegans*. The researchers observed that these flavonols increased the lifespan of the nematodes by 11% to 16% compared to the control group. Additionally, the flavonols improved reproductive parameters and increased the average body size of the nematodes. They also enhanced the resistance of the animals to juglone-induced oxidative stress, with the compounds' effectiveness depending on the nematodes' maturity stage. The researchers confirmed that the flavonols were absorbed by *C. elegans* through HPLC-DAD-ESI/MS analysis.[57]

Similarly, Kampkötter *et al.* reported that quercetin supplementation increased the lifespan of *C. elegans*. The treatment with quercetin also enhanced the nematodes' resistance to juglone-induced oxidative stress, resulting in increased survival and reduced reliance on Superoxide Dismutase-3 (SOD-3). The authors also observed an increase in the translocation of DAF-16 (FoxO) to the nucleus, similar to the findings with *E. oleracea* mentioned earlier. DAF-16 translocation is known to play a role in stress response and longevity regulation in *C. elegans*.[58]

A study by Li *et al.* demonstrated the potential of quercetin in ameliorating age-induced cognitive decline in senescence-accelerated mice. The researchers administered quercetin at two doses (35 and 70 mg/kg) for four months and assessed cognitive function using the Morris water maze paradigm. The results showed that quercetin treatment reduced cognitive decline compared to the untreated aging group. The authors attributed this effect to the decreased neuroinflammation and regulation of the Sirtuin1/NLRP3 pathway. They observed decreased expression of cleaved-caspase 1, IL-18, IL-1β, NLRP3, ASC, and increased expression of SIRT1, PSD95, BDNF, and NGF in the hippocampus of the quercetin-treated group compared to the untreated aging group.[59]

Jiang *et al.* investigated the effect of quercetin on endothelial senescence. They tested quercetin in ApoE-/- mice with atherosclerotic lesions and oxidized LDL-induced senescence in human aortic endothelial cells *in vitro*. The results showed that untreated animals had lipid deposition in arterial lumina, increased adhesion molecules (ICAM-1, VCAM-1), cytokines (IL-6), and decreased levels of SIRT1. However, quercetin treatment prevented these changes and decreased the expression of senescence-associated β-galactosidase. *In vitro*, quercetin improved the morphology of human aortic endothelial cells, reduced Reactive Oxygen Species (ROS) generation and cellular apoptosis, and increased mitochondrial membrane potential.[60] Kim *et al.* also conducted an *in vitro* study using vascular smooth muscle cells; they found that quercetin induced apoptosis specifically in senescent cells through AMP-activated protein kinase (AMPK) activation.[61] The review by Cui *et al.* provides a dedicated analysis of the anti-aging effects of quercetin.[62]

Other compounds found in *M. dubia* were reported to exert an anti-aging effect. The study by Baradaran Rahimi *et al.* explored the potential anti-aging effects of ellagic acid in a D-galactose-induced aging mouse model. The researchers assessed various biochemical and physiological parameters associated with aging and observed the effects of ellagic acid treatment. The results showed that D-galactose administration led to increased levels of IL-6, TNF-α, Malondialdehyde (MDA), Acetylcholinesterase (AChE), Advanced Glycation End products (AGEs), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Fasting Blood Sugar (FBS), and glycated Hemoglobin (HbA1c), while decreasing Glutathione (GSH), Brain-Derived Neurotrophic Factor (BDNF), Dehydroepiandrosterone Sulfate (DHEA-SO4), and testosterone. However, ellagic acid treatment at a dose of 30 mg/kg per day for ten weeks or a higher dose of 100 mg/kg per day for six weeks ameliorated these adverse effects associated with aging. The lower dose of ellagic acid exhibited a slower but significant improvement in the measured parameters, while the higher dose showed faster action. Interestingly, co-treatment with GW9662, an antagonist of Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ), hindered the protective effect of ellagic acid at the lower dose, suggesting that the activity of ellagic acid at this dose was dependent on PPAR-γ. However, the antagonist did not block the protective effects of ellagic acid at higher doses, indicating the involvement of additional mechanisms.[63]

The studies by Kharat *et al.* (2020) and Bai *et al.* (2022) provide further evidence for the potential anti-aging effects of ellagic acid.[64] Kharat *et al.* demonstrated that ellagic acid (200 μM) increased the longevity and maximum lifespan of *Drosophila melanogaster* and enhanced stress resistance against shock, starvation, and hydrogen peroxide. This was associated with increased expression of dFoxO, Catalase (CAT), and superoxide dismutase 2 (SOD2).[64] Similarly, Bai *et al.* found that ellagic acid (50 μM) extended the lifespan of *C. elegans* under various stress conditions, including ultraviolet radiation (36%), heat stress (36%), oxidative stress (155%), and *Pseudomonas aeruginosa* infection (80%). DAF-16 (FoxO) translocation into the nucleus was implicated in ellagic acid's effects in *C. elegans*.[65]

In addition to quercetin and ellagic acid, other compounds found in *M. dubia*, such as anthocyanins and ascorbic acid (Vitamin C), may contribute to its anti-aging effects. As mentioned earlier, anthocyanins possess antioxidant properties and have been associated with various health benefits. Ascorbic acid, on the other hand, acts as an antioxidant in the body and has been shown to mitigate oxidative stress, telomere attrition, chromatin disorganization, and excessive release of pro-inflammatory factors, which are all implicated in aging processes. Ascorbic acid has also been linked to the modulation of inflammaging and immunosenescence, two significant contributors to aging.[66]

Bixa orellana L. (Annatto, Urucum, Achiote)

Bixa orellana, commonly known as annatto, belongs to the family Bixaceae. It is native to South and Central America, primarily found in the Amazon Rainforest. South America is the largest producer of annatto (60%), followed by Africa (27%) and Asia (12%).[67-69] Brazil is the leading producer, with an annual production of approximately 12,000 tons.[70] The seeds of *B. orellana* contain pigments used since ancient times, including by the Aztecs, as body ink. Today, annatto pigments are extensively utilized in the food industry, textile industry, ink production, and cosmetics.[67,68]

B. orellana is an evergreen species that can reach heights of up to 9 m, depending on the local soil and temperature conditions. The inflorescences are white or pink and can occur in the first or second year of growth.[69,71] The fruits of *B. orellana* have a capsule shape and are covered with burrs on the surface. Numerous egg-shaped seeds are found inside the fruits, typically ranging from 30 to 45 seeds per fruit. These seeds are covered with a thin, deep reddish-orange layer, where most of the bioactive compounds are concentrated.[69]

Bixa orellana seeds are known for their intense dye, a rich source of carotenoids. The primary carotenoid compound found in annatto seeds is bixin (Table 1), with cis-bixin being the predominant form, accounting for approximately 80% of the total carotenoid content.[69,72,73] Other carotenoids in annatto seeds include norbixin (cis/trans), β-carotene, cryptoxanthin, lutein, zeaxanthin, and others. Bixin is classified as an apocarotenoid, a terpenoid derived from the oxidative cleavage of carotenoids. Its precursor is lycopene.[74]

In addition to carotenoids, annatto seeds contain tocotrienols and geranylgeraniol (Table 1). Tocotrienols and tocopherols belong to the family of compounds known as Vitamin E. These groups are stereoisomers with a similar structure, but tocotrienols have three double bonds in the carbon side chain, giving them better bioavailability and biological activity than tocopherols.[69] Geranylgeraniol is an isoprenoid compound found in annatto seeds and is an intermediate in cholesterol biosynthesis. It is involved in various physiological processes in the body.

Bixa orellana against aging

The study conducted by Gómez-Linton *et al.* is significant as it assessed the effects of an annatto-derived product, a lipophilic extract, on the lifespan of *C. elegans*. This study appears to be the first to investigate an annatto-derived extract's longevity properties. The results were promising, indicating that the treatment with the extract increased the median lifespan of *C. elegans* by 35% and the maximum lifespan by 27%. Furthermore, the extract enhanced the worms' oxidative and thermal stress resistance without adversely affecting their fertility. Importantly, the study also sheds light on the potential mechanism underlying the observed lifespan extension. The authors found that the increased lifespan was not attributed to caloric restriction but instead involved the insulin/IGF-1 pathway. This suggests that the annatto-derived extract may modulate this signaling pathway, which is known to play a crucial role in longevity regulation.[75]

The studies conducted by Makpol *et al.* and Khor *et al.* provide valuable insights into the potential anti-senescence effects of tocotrienols, major compounds from annatto.[76,77] Makpol *et al.* investigated the effects of a tocotrienol-rich fraction (origin not specified) on human diploid fibroblasts *in vitro*. They found that incubating the fibroblasts with the tocotrienol-rich fraction (0.5 mg/mL, 24 hr) resulted in a reversal of senescence-associated morphology, a decrease in senescence-associated beta-galactosidase (SA-β-gal) activity, DNA damage, and the frequency of cells in the G0/G1 phase. Additionally, the treatment increased the frequency of cells in the S phase, restored telomerase activity, and increased telomere length. These findings suggest that tocotrienols can potentially restore telomere length and reverse senescence-associated cell cycle arrest at the cellular level.[76]

In a separate study, Khor *et al.* examined the anti-senescence activity of a palm oil-derived fraction rich in Vitamin E isomers, including α-tocotrienol (26.89%), β-tocotrienol (3.64%), γ-tocotrienol (31.66%), δ-tocotrienol (13.66%), and α-tocopherol (24.15%). Using primary human fibroblasts, the researchers observed that cells in replicative senescence exhibited increased Reactive Oxygen Species (ROS) generation and lipid peroxidation. However, when treated with the tocotrienol-rich fraction, the cells showed enhanced antioxidant capacity and reduced free radical insults. These findings suggest that tocotrienols and other Vitamin E isomers can improve the antioxidant defenses of senescent cells, potentially mitigating the oxidative stress associated with cellular senescence.[77]

The studies conducted by Adachi and Ishii, Aan *et al.*, and Sien *et al.* provide further evidence for the potential lifespan-extending effects of tocotrienols *in vivo*, particularly in *C. elegans* models.[78,79] Adachi and Ishii investigated the effects of a tocotrienol-rich fraction, predominantly composed of α-tocotrienol (24%) and γ-tocotrienol (12%), on the lifespan of *C. elegans* exposed to Ultraviolet B (UVB) radiation. The researchers found that the tocotrienol-rich fraction significantly increased the lifespan of UVB-exposed nematodes compared to the control group. Furthermore, the fraction reduced protein carbonyl levels, indicating decreased oxidative damage. In contrast, α-tocopherol, a common form of Vitamin E, did not exhibit similar effects. These findings suggest that tocotrienols, specifically α-tocotrienol and γ-tocotrienol, have a lifespan-extending effect and can protect against oxidative damage induced by UVB radiation.[78]

Aan *et al.* examined the effects of another tocotrienol-rich fraction on the lifespan of *C. elegans*, particularly under conditions of

hydrogen peroxide-induced stress. The fraction, containing various tocotrienol isomers, significantly increased the mean lifespan of nematodes exposed to hydrogen peroxide compared to the hydrogen peroxide-treated group without the fraction. Notably, the nematodes treated solely with the fraction or fraction plus hydrogen peroxide exhibited the longest mean lifespan, even surpassing the control group not treated with hydrogen peroxide. Additionally, the fraction reduced the accumulation of lipofuscin, a marker of aging, and protein carbonyl levels. These results suggest that tocotrienols can enhance longevity and mitigate oxidative stress-associated damage in *C. elegans*.[79]

Sien *et al*. conducted a similar study using a tocotrienol-rich fraction consisting primarily of γ-tocotrienol (50 μg/mL). The researchers found that the fraction significantly increased the lifespan of *C. elegans* and enhanced their thermotolerance. However, the treatment did not improve the locomotion of aging nematodes. These findings suggest that γ-tocotrienol, as the predominant tocotrienol isomer in the fraction, plays a crucial role in promoting longevity and thermotolerance in *C. elegans*.[80]

The evidence suggests that tocotrienols potentially affect lifespan extension and senescence modulation. However, it is worth noting that most studies have utilized mixtures of Vitamin E compounds, and further research is needed to specifically examine the effects of tocotrienols alone, as the presence of tocopherols may impact tocotrienol bioavailability.[81]

In a study by Goon *et al*., the effects of treatment with α-tocopherol or tocotrienol capsules were investigated in older adults (50-55 years old) with respect to oxidative status. The tocotrienol capsules contained a mixture of tocotrienols (150 mg/day), including α-tocotrienol, β-tocotrienol, δ-tocotrienol, and γ-tocotrienol, along with α-tocopherol. The study's findings showed that both treatments reduced levels of Malondialdehyde (MDA), a marker of oxidative stress, after three and six months of treatment. Both treatments also decreased protein carbonyl levels after six months, but statistical significance was observed only in the group treated with α-tocopherol. Tocotrienols were found to reduce DNA damage levels, with significant differences observed only in women. Moreover, both treatments led to increased levels of Vitamin D.[82]

CONCLUSION

The aging process is characterized by the accumulation of senescent cells, which can contribute to the development of Age-Related Diseases (ARDs) and impact overall health. Here we review some plant species found in the Amazon, such as *Euterpe oleracea, Myrciaria dubia*, and *Bixa orellana*, that have been shown to possess properties that can combat deleterious effects of senescence.

The studies reviewed here provide valuable insights into the potential benefits of these plant species and their metabolites in preventing age-related cellular senescence and potential ARDs. The findings can guide future research efforts to investigate these plants further, aiming to develop nutraceutical or pharmaceutical products.

While promising pieces of evidence are obtained by using *C. elegans* as a model, more studies with vertebrates are required, specifically mammals. Additionally, although some studies have been performed with these species in human, aging and senescence per se has not yet been assessed and warrant further studies to explore these species as healthy aging-promoting agents.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ABBREVIATIONS

ARD: Age-related diseases; **ATM:** Ataxia-telangiectasia mutated; **ATR:** ATM and Rad3-related; **CDK:** Cyclin-dependent kinase; **DRRs:** Repair responses; **MDM:** Mouse double minute; **PRC:** Polycomb repressive complexes; **RB:** Retinoblastoma protein; **SA-β-gal:** Senescence-associated beta-galactosidase; **SASP:** Senescence-associated secretory phenotype; **SIPS:** Stress-induced premature senescence; **MRN:** Mre11/Rad50/NBS1; **mTOR:** Mammalian target of rapamycin; **NF-κB:** Nuclear-factor κB.

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