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REVIEW ARTICLE

Pitanga (*Eugenia uniflora L.*) as a source of bioactive compounds for health benefits: A review

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Abstract The pitangueira (*Eugenia uniflora*) is a tree native to Brazil but is cultivated in several subtropical countries. A great diversity of nutrients and bioactive compounds have been found in the leaves and fruits of *E. uniflora*, which supports its use in folk medicine to treat diseases such as stomach and intestinal disorders, fever and general inflammation. Antimicrobial, antiviral, antifungal and antioxidant effects on metabolism have been reported for this plant. This review discusses the phytochemical profile, toxicity and pharmacological action of *E. uniflora* leaves and fruits and points out that gaps in the literature that need to be investigated further. This review also discusses studies developed with *E. uniflora* demonstrating its promising therapeutic potential for several diseases with an apparent low toxicity in mammals. The compilation of the main pharmacological and toxicological results, as well as the phytochemical characterization of the varieties and constituents of *E. uniflora* are general aspects that this review attempts to demonstrate in order to contribute to the new approaches and developments to plant-derived natural product drug

Abbreviations: *A. salina*, *Artemia salina*; ABTS, 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic) acid; ACE, aqueous crude extract; AOPP, protein oxidation products; AqF, aqueous fraction; $a\beta_{1\text{-}42}$, amyloid β peptide fragment 1-42; *C. elegans*, *Caenorhabditis elegans*; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; *D. melanogaster*, *Drosophila melanogaster*; d.w, dry weight; DEX, dexamethasone; DMSO, dimethyl sulfoxide; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; *E. uniflora*, *Eugenia uniflora*; EAF, ethyl acetate fraction; EBV, Epstein-Barr virus; EC50, half maximal effective concentration; FRAP, Fe-reducing antioxidant potential; GAE, gallic acid equivalents; GSH, glutathione; HDPAF, high-polymerization Agave Frutans; HIV, human immunodeficiency virus; HPAF, high-performance Agave Frutans; i.c.v, intracerebroventricular; IC_{50}, half maximal inhibitory concentration; IL-1β, Interleukin-1 Beta; IL-8, Interleukin-8; iNOS, induced nitric oxide synthase; LD_{50}, lethal dose 50%; LOX, lipoxygenase; LPS, lipopolysaccharide; MD, maltodextrin; N2, wild type; NF-kB, nuclear factor-kB; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PCA, air-dried extract; PCS, ethanolic sun-dried extract; ROS, reactive oxygen species; SOD-3, superoxidodismutase-3; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TNF-α, Tumor Necrosis Factor-Alpha; VLDL, very low-density lipoprotein

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discovery. However, further studies are required to establish the nutraceutical effects and uses of *E. uniflora* as an important and safe supplement for human health.

Contents

1. Introduction

The *Myrtaceae* family is one of the main families of commercial fruit trees in the world, comprising approximately 121 genera (de Paulo Farias et al., 2020). The genus *Eugenia* is considered the fourth most important genus of the Myrtaceae family, it is estimated that 350 species are native to Brazil (de Souza Cardoso et al., 2018), in addition to ecological importance, the representative species of the *Myrtaceae* family are aromatic plants with large agro-industrial potential (Sardi et al., 2017).

The genus *Eugenia* is used in folk medicine to treat wounds, flu, fever, cough, gout, hypertension, digestive and liver diseases, rheumatism, tonsillitis, sore throat, hemorrhoids and diarrhea (Arai et al., 1999, de Araujo et al., 2019, Araujo et al., 2021). The most studied species of *Eugenia* is *E. uniflora L.*, producer of pitanga (*E. uniflora L.*) (Malaman et al., 2011).

The pitangueira (*E. uniflora L.*) is a tree with a dense crown, measuring between 2 and 9 m in height, branched, with a rounded shape, persistent foliage and deep root system (Sanchotene 1989, Lorenzi 2008) (Fig. 1). It is found primarily in the south and southeast regions of Brazil. However, it is also cultivated in subtropical areas of Latin America (Bicas et al., 2011). Brazil has the largest germplasm bank of *E. uniflora* conserved *ex situ*, although not all information is available as there has been no complete evaluation and characterization.

The leaves of *E. uniflora* are identified as simple opposites, with a petiole measuring approximately 2 mm. When the leaves are new, they have a brownish-green color and a membranous consistency, whereas the adult leaves are dark green in color (Fouqué 1981, Lorenzi 1998). Due to complexities including variability, biotype, environmental factors, and the region in which it is located, it is challenging to complete a phenolic profile and characterize the components of the *E. uniflora* leaf (Costa et al., 2010).

The flowers grow at the base of branches after an age of approximately one year. They comprise 4 to 8 hermaphrodite flowers that have a mild fragrance and produce little or no nectar. The flower comprises 4 free petals, cream white in color. The anthers are yellowish in color and abundant in pollen with white stylets (Sanchotene 1989).

The pitanga is the popular name of the fruit from the pitangueira. The name has an indigenous origin being derived from the term Tupy " pi'tãg which means red, referring to the most common color of the fruit (Donadio et al., 2002). However, this plant is also known as the Brazilian cherry or Suriname cherry (Fiuza et al., 2008). Generally, pitanga fruits are berry-shaped and have 8–10 longitudinal furrows in the skin (Romagnolo and Souza 2006). They are composed of 77% pulp and 23% seed and have a unique sweet, acid flavor with an intense aroma (Köhler 2014). The pitanga fruit can be consumed raw or used in juices, ice creams, sweets, liquors, and jellies (Coradin et al., 2011).

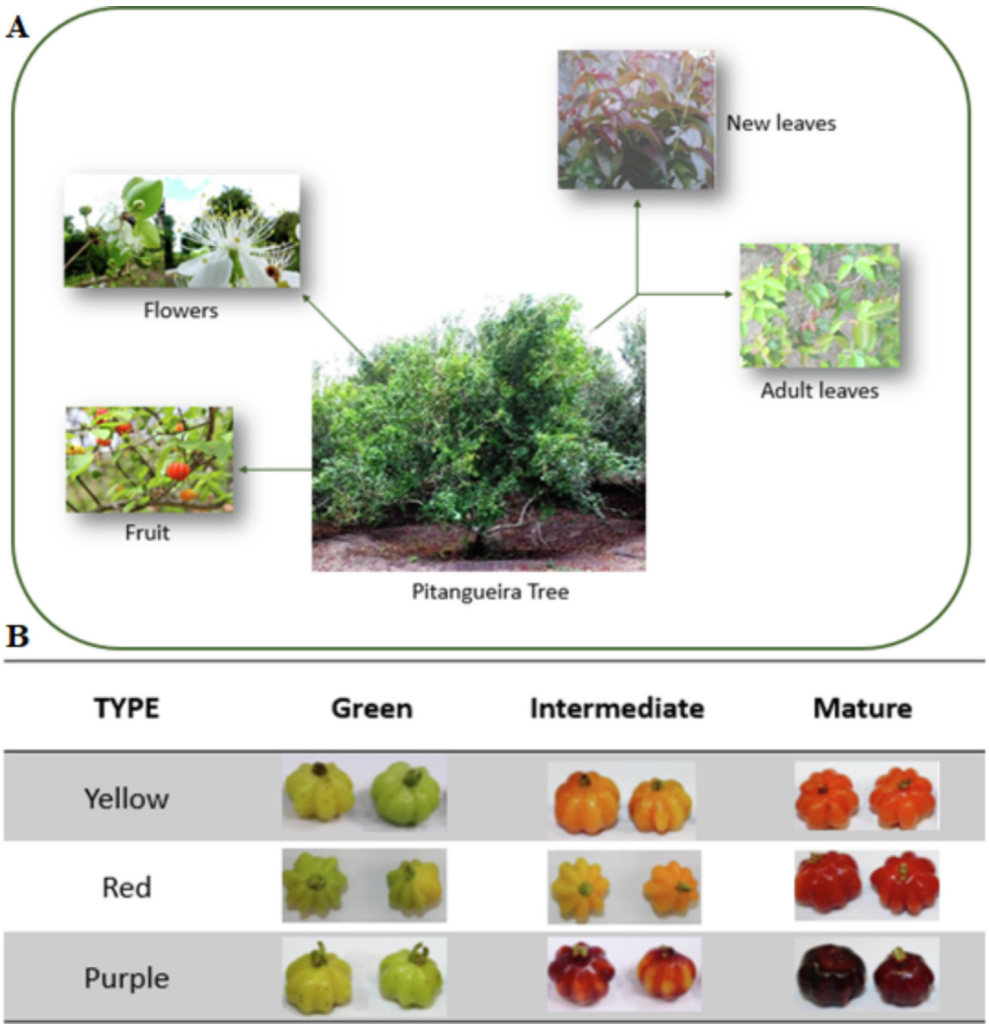

Fig. 1 The Pitangueira tree, its parts, varieties and different berries according to the stage of maturation and the variety. A) Images adapted from the Pitangueira Book (Júnior et al., 2007). B) Ripening stages of the different types of pitanga (*E. uniflora* fruit) (Souto, 2017).

Pitanga has different berries according to the stage of maturation and the variety. The extensive genetic diversity is primarily manifested in the color of the ripe fruit (Silva 2006, Bezerra et al., 2018). During ripening, the fruit's epicarp evolves from green to orange and red to dark purple (de Lira Júnior et al., 2007) (Fig. 1). Therefore, the fruits undergo changes not only in its color but also in its phytochemical constituents.

Several studies have evaluated the therapeutic efficacy of extracts derived from this plant through different extraction methods in several experimental models, however, this data from different varieties have never been analyzed altogether (Soares 2014, Falcao et al., 2018, Tambara et al., 2018). This narrative review was carried out as a literature review in 2021 and includes articles published from 1976 to 2021. Specialized databases (Web of Science, Scielo, Pubmed, Science Direct, Scopus and selected articles from Google Scholar), were used and included *E. uniflora, E. uniflora* purple, *E. uniflora* red, *E. uniflora* yellow as keywords for literature search. In this review, the phytochemical characteristics of *E. uniflora* will be addressed along with its toxic potential. In addition, the pharmacological properties of leaves and fruits of different varieties of *E. uniflora* will be described.

2. Physical-chemical characterization of *E. uniflora* varieties

It has been demonstrated that *E. uniflora* leaves contain constituents such as anthraquinones, steroids, triterpenes, flavonoids, saponin heterosides, and tannins (Brasileiro et al., 2006, Fiuza et al., 2008). Additionally, the fruits present a significant number of bioactive compounds, such as catechins, flavonols, proanthocyanidins, and carotenoids (Santos et al., 2003, Hoffmann-Ribani et al., 2009, Celli et al., 2011, Denardin et al., 2015, Souto 2017). The pulp presents low calories and contains calcium, phosphorus, iron, and vitamins B1, B2, and C (Helt et al., 2018).

Among the different types of pitanga, the red variety is richer in carotenoid compounds, such as beta-carotene and lycopene as well as in the flavonols myricetin, kaempferol and quercetin (Hoffmann-Ribani et al., 2009). In smaller quantities, these bioactive compounds are also found in yellow pitanga (Souto 2017). Generally, the higher amounts of carotenoids and phenolic compounds gives the purple variety the best antioxidant potential (Celli et al., 2011, Denardin et al., 2015).

It is noteworthy that many factors influence the phytochemical composition of these plants, such as environmental conditions or soil characteristics. For instance, the climate influences the carotenoid composition of pitanga fruit and its phenolic compounds (Robards and Antolovich 1997). A study of mature fruits from 12 randomly selected sister seedlings of purple pitanga demonstrated that there existed differences between the content of myricetin, quercetin, and lutein in the different samples, which exemplifies the variability in the constituents of the fruits belonging to the same plant (Griffis et al., 2013).

The ripening of the fruits is related to the presence and quantity of pigments, such as carotenoids, which may have increased synthesis according to the maturation stage and mainly due to the warm climate (Santos et al., 2003, Bagetti et al., 2011). In a study developed by Santos et al. (2003), the maturation stages of the fruits were classified into six, these maturation stages were compared using the red and purple pitanga varieties. The purple pitanga variety has six maturation stages, which is more than the red type, which has five (Dos Santos et al., 2018).

Factors including the storage time that can influence pulp characteristics, causing reduction in the carotenoid amount (Lopes et al., 2005), plant part selection (for example leaf, whole fruit, fruit pulp or peel) (de Lima et al., 2002), pre-extraction steps (drying, grinding, pressing, etc.), and the extraction method (Figueirôa et al., 2013) must be well considered as they influence the quantity and stability of the phytochemicals (Kumar and Sharma 2018).

2.1. Characterization of the leaves

Although some studies have already demonstrated the effects of *E. uniflora*, little data in the literature presents the identification of the phytochemicals present in the plant's leaves. In addition, the knowledge about a possible correlation between phytochemicals and the biological activities of this plant is still insufficiently evidenced because of the lack of studies (Falcao et al., 2018).

A phytochemical analysis by Brasileiro et al. (2006) demonstrated that *E. uniflora* leaves contain alkaloids, triterpenes, tannins, flavonoids, and anthraquinones. Furthermore, high concentrations of volatile organic compounds germacrene B (9.60%), γ-elemene (7.97%), β-elemene (9.26%), germacrene D (6.46%), γ-muurolene (5.2%) and β-caryophillene (5.17%) were found in the leaves from purple pitangueira (Mesquita et al., 2017). Furthermore, Chang et al. (2011) demonstrated curzerene presence at 85.1%, the same amount reported by Costa et al. (2009).

Notably, substance from the pitangueira leaves of Rio de Janeiro (50.2%, Melo et al., 2007), Goiás (42.6%, brilliant red fruit pitangueira) (Costa et al., 2010), Goiás (34.8%), (Peixoto et al., 2019) and Nigeria (19.7%) (Ogunwande et al., 2005) were also found to be the primary component in essential oils.

Other classes of compounds are also present but to a lesser extent (less than 20% in the leaves), such as monoterpene hydrocarbons, oxygenated monoterpenes and oxygenated sesquiterpenes (Apel et al., 2004, Costa et al., 2010). The presence of flavonoids and phenolic compounds has been reported in the *E. uniflora* leaves ethanolic extract as described by Fiuza et al. (2008).

Table 1 Chemical components of different extracts of *E. uniflora* leaves.

Extract	Total phenolic (mg GAE.g^{-1})	Flavonoid content (mg QE.g^{-1})
Ethyl acetate fraction of leaves	2756 ± 15.5	84.3 ± 3.4
Butanol fraction of leaves	2492 ± 58.1	8.6 ± 0.9
Aqueous fraction of leaves	2445 ± 15.5	2.1 ± 0.07
Ethyl acetate fraction of leaves	2831 ± 23.0	31.2 ± 1.1

See Table adapted from Figuerôa et al. 2013. GAE = gallic acid equivalents and QE = quercetin equivalents.

Besides, Figuerôa et al. (2013) demonstrated in an experimental study using different extractors from *E. uniflora* leaves that the total phenolic content was similar between the different types of extracts. However, the flavonoid content showed substantial differences that can significantly influence the pharmacological properties of these extracts. Thus, it is noteworthy that the extraction method also markedly influences the phytochemical constitution of the extract (Table 1).

A recent study by Sobeh et al. (2020) showed a more comprehensive phytochemical profile of the ethyl acetate fraction (EAF) of red *E. uniflora* leaves, which presented an extensive variety of polyphenols, such as quercetin, myricetin, apigenin and kaempferol glucosides. This extract seems to present promising properties due to this composition. Other studies using methanol extract of the leaves of *E. uniflora* and LC-MS/MS chromatography have identified about 17 compounds among which are secondary metabolites: gallic acid 3-O-[6′-O-acetyl-β- D-glucoside], myricetin-3-O-β-D-glucoside, myricetin-3-O-β-D-galactoside, myricetin-3-O-[6′-O-β-N-acetyl galacto-side], myricetin-3-O-rhamnoside, myricetin-3-O-[3′-O-acetylrhamnoside], myricetin-3-O-[2′-O-acetyl-α-L-rhamno side], quercetin-3,5-dimethyl ether, ellagic acid, 2,3-hexahy droxydiphenoyl-D-glucose, gallic acid, methylgallate, 3-O-D-galloylglucose, 2-O-D-galloylglucose, gentistic acid 5-O-β-D-glucoside, gentistic acid 5-O-[6′ -O-β-D-galloyl glucoside], valoneic acid dilactone (Sobeh et al., 2019).

2.2. Purple E. uniflora fruits

Purple pitanga is the rarest variety but has a higher amount of total phenolics and therefore higher antioxidant properties than other pitanga types (Weyerstahl et al., 1988). The purple *E. uniflora* fruit has approximately twice the phenolic content compared to the red type (463 ± 16 to purple and 210 ± 3 % mg galic acid (GA). 100 g^{-1} to red fruit) This has promoted an increasing scholarly interest in this variety (Bagetti et al., 2011). The purple pitanga variety presents higher pH and higher total soluble solids and carbohydrates (Table 2). Furthermore, regarding fatty acid content, it has been described that oleic acid is present in a higher proportion than others (monounsaturated and polyunsaturated fatty acids). It has been found to have a high phenolic content in the methanolic extract, and a considerable amount of anthocyanins in the ethanolic extract has been detected (Bagetti

Table 2 Chemical characteristics and bioactive compounds found in the maturation of purple and red *E. uniflora* fruits.

Characteristics according to stage of maturation *E. uniflora* fruits						
Parameters	Maturation stages (purple / red type)					
	1	2	3	4	5	6
Diameter [A]	17.9 / 19.9	17.8 / 21.4	17.8 / 21.7	17.8 / 22.4	17.0 / 21.2	17.6 / nd
Length [A]	14.3 / 13.2	13.9 / 14.3	15.1 / 15.0	15.0 / 15.1	14.6 / 14.6	15.1 / nd
Fresh weight [B]	2.56 / 3.54	2.56 / 4.25	2.96 / 4.65	3.37 / 5.25	2.67 / 4.40	3.32 / nd
Dry matter [C]	26.26 / 19.02	24.7 / 19.44	22.36 / 18.26	23.51 / 17.83	22.86 / 18.81	24.41 / nd
Seeds [C]	35.26 / 27.61	28.20 / 29.69	27.64 / 23.86	30.93 / 20.41	34.26 / 25.04	38.23 / nd
Soluble solids [C]	8.53 / 8.13	9.73 / 8.96	10.76 / 10.33	12.53 / 11.00	10.56 / 12.56	13.04 / nd
Acidity [D]	1.66 / 0.86	1.74 / 1.23	1.98 / 1.61	1.55 / 1.58	1.73 / 1.57	1.64 / nd
pH	3.38 / 3.36	3.29 / 3.11	3.24 / 3.13	3.43 / 3.16	3.28 / 3.28	3.55 / nd
Vitamin C [E]	21.85 / 22.50	29.15 / 29.93	32.85 / 40.65	42.65 / 51.00	55.00 / 33.00	38.5 / nd
Total Anthocyanins [E]	0.00 / 0.00	2.40 / 0.09	9.40 / 0.29	16.30 / 0.51	21.60 / 0.98	29.60 / nd

Characteristics according to maturation stage of the purple and red pitanga. 1 – Green; 2 – Breaker (starting to change shell's color); 3 – Beginning of purple pigmentation; 4 – Partially purple; 5 – Completely purple; 6 – Dark purple. nd - values not described. Source: dos Santos et al., 2002. Data are expressed as [A] mm, [B] g, [C] %, [D] % citric acid and, [E] mg.100 g^{-1}.

et al., 2011). Accordingly, this can be associated with greater antioxidant capacity as demonstrated by the DPPH method (Celli et al., 2011).

The anthocyanins present in fruits such as pitanga are very promising for beneficial effects on human health. Some studies report that the intake of these compounds in humans is estimated to be 180–215 mg.day^{-1} in the USA (Kuhnau 1976). A profile characterization of anthocyanins in the ethanolic extract of purple pitanga revealed the presence of five anthocyanins: delphinidin 3-O-glucoside (99.65 ± 1.77 mg.100 g^{-1} lyophilized fruit), cyanidin 3-O-glucoside (512.01 ± 11.18 mg.100 g^{-1} lyophilized fruit), pelargonidin 3-O-glucoside (2.16 ± 0.13 mg.100 g^{-1} lyophilized fruit), cyanindin 3-O-pentoside (0.83 ± 0.07) and cyanidin derivative (5.16 ± 1.23 mg.100 g^{-1} lyophilized fruit) (Tambara et al., 2018). These anthocyanins seem to be very stable after freezing unlike other plant constituents (Lima et al., 2005). Furthermore, the peel has been found to contain more anthocyanins, flavonoids, and carotenoids compared to the pulp: Total Anthocyanins (mg.100 g^{-1}) – 26 ± 0, Total Flavonoids (mg.100 g^{-1}) – 18 ± 0, Total Carotenoids - (μ.g^{-1}) 111 ± 2 (de Lima et al., 2002).

2.3. Red E. uniflora fruit

The general properties of *E. uniflora* red fruit variety are characterized by lower pH, acidity, carbohydrates and phenolic content when compared to the purple type (Table 2). According to data from Denardin et al. (2015), a red pitanga has about 5.86 ± 0.03 ug of β-carotene.g^{-1}. Carotenoids are natural pigments produced during the photosynthetic process that provides coloring for flowers and fruits. These have some ingredients that can potentially prevent cardiovascular disease and cancer. Therefore, the investigation of these compounds has expanded in recent years (Yuan et al., 2015).

One study found the concentration at 0.086 ± 0.00 mg GAE.100 g^{-1} of ascorbic acid and the total phenolic content of the ethanolic extract at 433.84 ± 60.5 mg GAE.100 g^{-1} fw (fresh weight) as determined by the Folin-Ciocalteu method adapted from Swain and Hillis (Denardin et al., 2015). This difference in values in relation to Table 2 can be attributed to a series of processes related to the stage of maturation at harvest, genetic variants, post-harvest management, storage, and processing conditions (Szeto et al., 2002).

It is known that there is a difference in the quantification of these compounds according to the pitanga variety. However a difference is also found when using other methods for the detection of phenolic compounds. It is noteworthy that phenolic compounds are secondary metabolites widely found in vegetables, fruits, leaves and fruits and may vary depending on soil composition, temperature, season, etc. Therefore, phenolics composition varies across different studies (Sobeh et al., 2019).

A chromatographic analysis of the ethanolic extract of the red fruit performed on HPLC-DAD (wavelength at 280 nm and 360 nm) demonstrated the presence of gallic acid and derivatives, quercetin and derivatives, quercetin-3-b-D-glucoside, quercetin-3-rhammoside, kaempeferol derivative, cyanidin-3-glucoside, cyanidin derivative and malvidin derivative (Denardin et al., 2015).

2.4. Yellow E. uniflora fruit

Few data in the literature provide information about the components present in the yellow *E. uniflora* variety (fruits and leaves). Souto et al. (2017) assessed the phytochemical composition of the methanolic extract of the yellow *E. uniflora* fruit, which included the presence of quercetin, myricetin and its derivatives: 1) In Green stage (mg.100 g^{-1} d.w): quercetin (43.3 ± 3.4), quercetin-3-glucoside (26.4 ± 5.3), myricetin (62.4 ± 8.2), kaempferol (1.5 ± 0.4); 2) In mature stage (mg.100 g^{-1} d.w): quercetin (20.1 ± 2.1), quercetin-3-glucoside (6.7 ± 1.8), myricetin (25.0 ± 3.6), kaempferol (ND). Additionally, the content of flavonoids with respect to the stages of development do not show significant changes with myricetin being the majority compound corresponding to 48% of the total flavonoids followed by quercetin with up to 39% of the total compared to the other flavonols.

On the other hand, the phenolic content changed depending on the development stage of the fruit. In the green maturation stage, the values obtained were approximately 35 mg GAE.g^{-1} d.w (dry weight), in the intermediate stage approximately 25 mg GAE.g^{-1} d.w and in the mature fruit approximately

15 mg GAE.g^{-1} d.w. The presence of ellagic acid was also detected at the mature stage (around 485.1 mg.100 g^{-1} d.w). In the earlier maturation stages, carotenoids such as ß-carotene and lycopene are not present. They are produced at the ripest stage of the fruit before changing to the next color (7.4 ± 3.1 μg.g^{-1} dw; 20.5 ± 5.2 μg.g^{-1} dw, respectively), other compounds as citric, succinic and malic acids were also found in the yellow cherry as demonstrated by Souto et al. (2017).

The lack of studies on the yellow pitanga hinders the discussion of this topic, it is evident that the preferential research on the red and purple pitanga is due to the strong presence of phenolic compounds, anthocyanins and carotenoids, since they present some photoprotective ingredients that can potentially prevent diseases related to oxidative damage. The low amount of carotenoids in the yellow pitanga can be a limiting factor for studies with this variety.

2.5. Non-volatile and volatile compounds

The constituents of plants directly influence the characteristics of their fruits. The presence of volatile organic compounds (VOCs) is responsible for the aroma and consequently the flavor of fruits. Some studies also demonstrate the influence of non-volatile compounds in the flavor of these fruits (Bai et al., 2016). Many factors can influence the presence of these compounds, such as climatic and growing conditions, in addition to the ripening stage of the fruit (Kawahata et al., 1996). Some authors used different methodologies to identify volatile and non-volatile compounds present in the constituents of pitangueira, as shown in Table 3. In addition, Fig. 2 shows the structures of the main bioactive compounds present in the constituents of pitangueira.

The main limitation of these studies is that many do not report the variety of the fruit or plant from which the compound was isolated, as well as its constituents. Only one study that demonstrated the presence of non-volatile compound cyanidin-3-glucoside used liquid chromatography-mass spectrometry (LC/MS) (Brasileiro et al., 2006). Many authors used the gas chromatography–mass spectrometry (GC/MS) to isolate the volatile compounds (Oliveira et al., 2008, Soares 2014). Mesquita et al., (2017) determined the volatile profiling through solid-phase microextraction (HS-SPME), combined with gas chromatography-mass spectrometry (GC–MS).

In the different maturation stages, terpenoids (monoterpenes and sesquiterpenes) are found. However, the presence of esters only was determined in the last stages of maturation (da Silva et al., 2019). In addition, it was observed that the different varieties of *E. uniflora* are responsible for the variability in the volatile compounds present in the leaves of the plant. The orange[1] variety of pitanga presents a high amount of hydrocarbon monoterpenes in relation to the purple and red that present similar profile (Mesquita et al., 2017). Some compounds, such as selin-1,3,7(11)-trien-8-one, are also found in the fruit extract (Oliveira et al., 2008). The presence of selina-1,3,7(11)-trien-8-one, curzerene and atractylone, spathulenol and germacrone were identified in specifically in red-orange[1], red and purple, respectively. It has been identified that the increase in the presence of anthocyanins and tannins decrease during the maturation process of pitanga (Ramalho et al., 2019).

The differences of climate conditions can exert influence on the chemical constituents of *E. uniflora*. The prevalence of monoterpenes is related in the pitanga fruits, but differences in relation to majority compound are observed in fruits cultivated in Brazil and Cuba, with the presence of *trans*-b-ocimene (36.2%) and curzenene (38,9%), respectively (Pino and Correa 2003, Oliveira and Padilha 2007). In addition, different seasons in the same country have been shown to affect the constitution of essential oils in the leaves of the plant. In the dry season, the essential oil of the leaves of *E. uniflora* of the red–orange variety presented as major compounds spathulenol (10%) and caryophyllene oxide (4.1%). However, in the wet season, the main major constituent was seline-1,3,7(11)-trien-8-one epoxide (29%) (Costa et al., 2009).

3. *E. uniflora* toxicity

Little is known about the potential toxicity of *E. uniflora* extracts and the essential oils from this plant. It is known that the seeds are extremely resinous and should not be ingested. Additionally, it has been known to cause diarrhea in dogs fed with the whole fruits and the strong, and the spicy scent emanating from bushes being pruned has been known to irritate the respiratory tract of allergic people (Morton 1987).

In mice, a single oral administration of the essential oil obtained from the leaves of *E. uniflora* at different doses (10, 50, 100 and 200 mg.kg^{-1}) did not cause death in any subject. Therefore, the lethal dose 50% (LD_{50}) was estimated to be greater than 200 mg.kg^{-1} (Victoria et al., 2012). Besides, the single administration of the leaves' essential oil did not induce any signs of toxicity in mice, such as weight change or loss of appetite (Victoria et al., 2012). Similarly, Schmeda-Hirschmann et al. (1987) demonstrated that the hydro-alcoholic extract of the leaves did not produce any signs of acute or subacute toxicity in mice orally receiving doses of up to 4200 mg.kg^{-1}.

A toxicity test was performed 14 days after a single oral administration of *E. uniflora* hydro-alcoholic leaf extract at different concentrations (3.0, 3.6, 4.3, 5.2 and 6.2 g.kg^{-1}) in mice (Auricchio et al., 2007). The first deaths occurred in the first 24 h in the animals treated with the higher dose. By the fourth day, a small percentage of the animals treated with the two highest doses died. On the sixth day of observation, the surviving animals recovered and no difference in the behavior of treated animals was observed. At the end of the study, no differences were observed in the general appearance (color, size) of removed organs such as heart, lung, liver and kidneys. Furthermore, no alterations in the relative masses of these organs removed from treated animals were observed compared to controls. The LD_{50} estimated was 5.93 g.kg^{-1}. In another study assessing chronic exposure to crude extract of *E. uniflora* fruit at the dose of 200 mg.kg^{-1}.day^{-1} for 21 days, no signs of toxicity were observed in rats (de Souza Cardoso et al., 2018). Accordingly, it can be suggested that overall, *E. uniflora* fruit extract has low toxicity for mammals.

However, toxicity studies with the ethanolic leaf extract in *Artemia salina* (*A. salina*) have recently shown moderate toxi-

[1] Corresponds to yellow variety of pitanga.

Table 3 Volatile and non-volatile compounds present in the constituents of pitangueira

Pitanga varieties	Plant Constituent	Volatile compound	Authors
Purple-	Pulpleaf	oxidoselina-1,3,7(11)-trien-8-one	Soares et al., 2015; Weyerstahl 1988
Purple	Pulp	selina-1,3,7(11)-trien-8-one	Soares et al., 2015
Purple	Pulp	oxidoselina-1,3,7(11)-trien-8-one	Soares et al., 2015
-	Fruit	Propyl acetate	Oliveira et al., 2006[F3]
-	Fruit	Ethyl propionate	Oliveira et al., 2006
-	Fruit	Isobutyl acetate	Oliveira et al., 2006
-	Fruit	n-Butyl acetate	Oliveira et al., 2006
-	Fruit	3-Methyl butyl acetate	Oliveira et al., 2006
-	Fruit	1,5,8-p-Menthatriene	Oliveira et al., 2006
-	Fruit	*trans*-β-Ocimen	Oliveira et al., 2006
-	Fruit	p-Mentha-1,5,8-triene	Oliveira et al., 2006
-	Fruit	Rosefuran	Oliveira et al., 2006
-	Fruit	β-Ocimene	Oliveira et al., 2006
-	Fruit	Acetophenone	Oliveira et al., 2006
-	Fruit	Germacrene-D	Oliveira et al., 2006
-	Fruit	Caryophyllene oxide	Oliveira et al., 2006
-	Fruit	α-Thujene	Pino et al., 2003
-	Fruit	α -Pinene	Pino et al., 2003
-	Fruit	β-Pinene	Pino et al., 2003
-	Fruit	β -Myrcene	Pino et al., 2003
-	Fruit	λ-Terpinene	Pino et al., 2003
-	Fruit	Terpinolene	Pino et al., 2003; Silva et al., 2019
-	Fruit	Allo-ocimene	Pino et al., 2003
-	Fruit	β-Elemene	Pino et al., 2003; Silva et al., 2019
-	Fruit	β-Caryophillene	Pino et al., 2003
-	Fruit	λ-Elemene	Pino et al., 2003; Silva et al., 2019.
-	Fruit	β-Elemenone	Pino et al., 2003
-	Leaf	α-Terpinene	Weyerstahl 1988
-	Leaf	*p*-Cymene	Weyerstahl 1988
-	Leaf	*trans*-Ocimene	Weyerstahl 1988
-	Leaf	*cis*-Ocimene	Weyerstahl 1988
-	Leaf	Linalool	Weyerstahl 1988
-	Leaf	Curzerene	Weyerstahl 1988
-	Fruit	Dracunculifoliol	Silva et al., 2019
-	Fruit	Heptanol	Silva et al., 2019
-	Fruit	Hexenol	Silva et al., 2019
-	Fruit	Cedrenal	Silva et al., 2019
-	Fruit	Hexanal	Silva et al., 2019
-	Fruit	Isovaleraldehyde	Silva et al., 2019
-	Fruit	Ethyl acetate	Silva et al., 2019
-	Fruit	Ethyl butanoate	Silva et al., 2019
-	Fruit	Ethyl hexanoate	Silva et al., 2019
-	Fruit	Turmerone	Silva et al., 2019
-	Fruit	Aromadrendene	Silva et al., 2019
-	Fruit	Cadinene	Silva et al., 2019
-	Fruit	Carene	Silva et al., 2019
-	Fruit	Cymene	Silva et al., 2019
-	Fruit	Epizonarene	Silva et al., 2019
-	Fruit	Germacren	Silva et al., 2019
-	Fruit	Guaiene	Silva et al., 2019
-	Fruit	Limonene	Silva et al., 2019
-	Fruit	Maaliol	Silva et al., 2019
-	Fruit	Ocimene	Silva et al., 2019
-	Fruit	Sylvestrene	Silva et al., 2019
-	Fruit	Tricyclene	Silva et al., 2019
-	Fruit	Valerianol	Silva et al., 2019
Orange*, Red and Purple	Leaf	3-hexen-1-ol acetate	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	α -phellandrene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	methyl salicylate	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	(Z)-3-hexenyl butyratea	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	α-copaene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	α-gurjunene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	α-humulene	Mesquita et al., 2016

(*continued on next page*)

Table 3 (*continued*)

Pitanga varieties	Plant Constituent	Volatile compound	Authors
Orange*, Red and Purple	Leaf	allo-aromadendrene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	β-selinene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	γ-muurolene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	α-amorphene	Mesquita et al., 2016
Orange*, Red and Purple	Leaf	ledol	Mesquita et al., 2016
Non-Volatile compound			
Purple	Pulp	cyanidin-3-glucoside	Soares et al., 2015

* Orange pitanga corresponds to yellow variety.

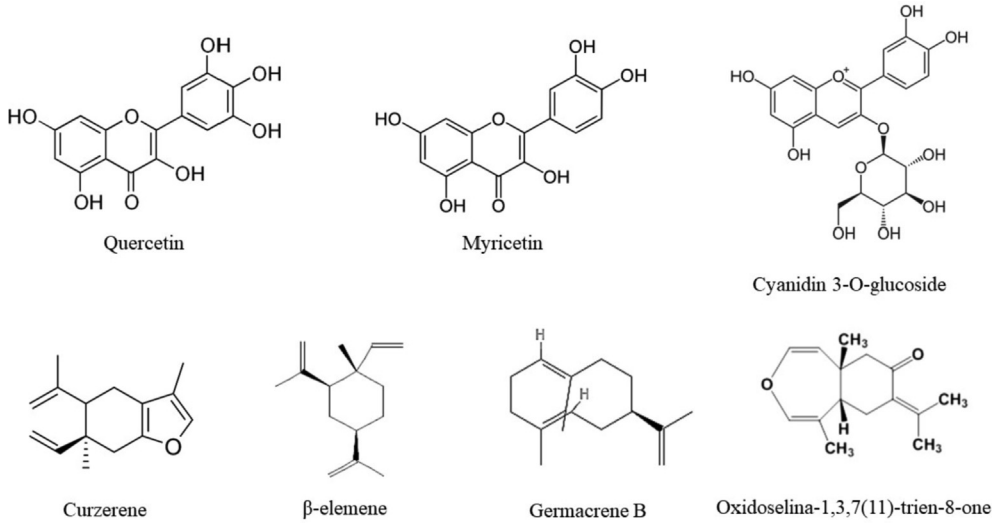

Fig. 2 The chemical structures of the main bioactive compounds present in the constituents of pitangueira.

city in this crustacean according to the criteria established by Déciga-Campos et al. (2007) with a lethal concentration 50% (LC_{50}) of 0.61 mg.mL^{-1} (Bobadilla et al., 2018). Montanher et al. (2002) obtained an LC_{50} higher than 1 mg.mL^{-1} for *E. uniflora* ethanolic extract in the same species. Additionally, Arcanjo et al. (2012) demonstrated that the ethanolic extract of the aerial parts contained a LC_{50} of 0.288 mg.mL^{-1} in *A. salina*.

In *Drosophila melanogaster* (*D. melanogaster*), Da Cunha et al. (2015) demonstrated that a short period of exposure to low concentrations of essential oil from *E. uniflora* leaves induced mortality and locomotor deficits by inducing oxidative stress. Moreover, De Carvalho et al. (2017) recently demonstrated for the first time that *E. uniflora* essential oil can induce mitochondrial dysfunction as well as to compromise mitochondrial respiration in *D. melanogaster*.

In vivo studies using the nematode *Caenorhabditis elegans* (*C. elegans*) have demonstrated that animals treated with red and purple pitanga fruit ethanolic extract 1%(v/v) showed no signs of toxicity either in short- or long-term assessments (Borges 2015). Similarly, Tambara et al. (2018) also demonstrated that treatment with purple pitanga fruit extract did not alter the worms' survival and reproduction at different concentrations (5, 50, 100, 250 and 500 μg.mL^{-1}).

Overall, it seems that very little is known about the toxic effects of *E. uniflora* extracts in mammalian models. However in invertebrate animals, it seems that the extracts are more toxic and may even compromise cellular respiration, depending on the part used (fruit or leaf) and the extraction method used. This toxic outcome has been associated with the insecticidal activity of *E. uniflora* extract (Jung et al., 2013) due to the presence of flavonoids and tannins identified in the plant's hydroalcoholic extracts (Auricchio et al., 2007). Tannins significantly reduce the growth and survival of insects by inactivating digestive enzymes and creating a complex of difficult-to-digest tannin-proteins (Melo et al., 2007). Therefore, further studies are required to clarify the possible toxicological mechanisms of the components of this plant.

4. Biological effects of *E. uniflora*

4.1. Antibacterial activity

Infections caused by bacteria are a significant public health concern. Multi-resistant microorganisms are present in hospitals and in other places. The investigation of new molecules in natural products that can kill resistant microorganism

species presents a plethora of possibilities. This property has been found for *E. uniflora* and has been explored in different scenarios.

A study evaluating the *in vitro* antibacterial activity of the hydroalcoholic extract of ripe *E. uniflora* demonstrated that it reduced the biofilm formation of *Streptococcus mutants*, *Streptococcus oralis* and *Lactobacillus casei*, with a reduction in bleeding caused by gingivitis, which was attributed to its anti-inflammatory action due to the presence of flavonoids (Jovito Vde et al., 2016). *Streptococcus mutans*, *Streptococcus sanguis*, *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus oralis* are involved in the biofilm formation and consequently cause predisposition to cavities. The ethanolic extract of the mature and unripe fruits as well as leaves extracts showed antibacterial activity, with the exception of the essential oil derived from the leaves (Oliveira et al., 2008).

In addition, another study with the essential oil from *E. uniflora* leaves demonstrated antimicrobial activity against *Staphylococcus aureus* and *Listeria monocytogenes*. These bacteria are part of the gram-positive group, whereas no effect was observed in the gram-negative pathogens (Victoria et al., 2012). Similarly, the essential oils were found to have bactericidal effect against other gram-positive pathogens, such as *Bacillus subtilis*, *Streptococcus faecalis* and *Staphylococcus albus*. Whereas no effect on the gram-negative group was found (Thambi et al., 2013). In gram-negative bacterias (*E. coli)* this oil present inhibitory effect and increase the activity of antibiotic aminoglycosides (Pereira et al., 2017).

On the other hand, positive results of *E. uniflora* against gram-negative bacteria were reported with ethanolic extract of the leaves, and inhibition was effective against *Enterobacter cloacae*, *Escherichia coli, Pseudomonas aeruginosa* and *Serratia marcescens* (Table 4) (Fiuza et al., 2009). Furthermore, pitanga seed have been found to have biological properties against both gram-negative and gram-positive pathogens. The essential oil and seed extracts present similar antibacterial properties due to the presence of oxygenated groups in the structure of the isolated compounds such as terpenoids, which may be responsible for this potential (Santos et al., 2015).

E. uniflora seeds contain lecithin that binds to microorganisms such as bacteria and can inhibit the growth of *Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella spp* at

Table 4 Antibacterial activity in different samples of *E. uniflora*.

Sample	Concentration	Bacteria	Inhibition zone (mm)	Reference
HEEU	0.3 $g.mL^{-1}$	*S. mutans*	14.0	Jovito et al., 2016
HEEU	0.3 $g.mL^{-1}$	*S. oralis*	23.0	Jovito et al., 2016
HEEU	0.3 $g.mL^{-1}$	*L. casei*	26.0	Jovito et al., 2016
EOL	5 $\mu g.mL^{-1}$	*S. aureus*	11.0	Thambi et al., 2013
EOL	5 $\mu g.mL^{-1}$	*B. subtilis*	12.0	Thambi et al., 2013
EOL	5 $\mu g.mL^{-1}$	*S. faecalis*	12.0	Thambi et al., 2013
EOL	5 $\mu g.mL^{-1}$	*S. albus*	12.0	Thambi et al., 2013
EOL	0.875 $g.mL^{-1}$	*S. aureus*	25.0	Fiuza et al., 2008
EOL	0.175 $g.mL^{-1}$	*E. coli*	16.0	Fiuza et al., 2008
EOL	0.0043 $g.mL^{-1}$	*P. aeruginosa*	25.0	Fiuza et al., 2008
EUS	1.5 $\mu g.mL^{-1}$	*S. aureus*	20.0	(Oliveira et al., 2008)
EUS	1.5 $\mu g.mL^{-1}$	*P. aeruginosa*	18.6	(Oliveira et al., 2008)
EUS	1.5 $\mu g.mL^{-1}$	*Klebsiella sp*	19.6	(Oliveira et al., 2008)
EUS	1.5 $\mu g.mL^{-1}$	*E. coli*	12.0	(Oliveira et al., 2008)

HEEU = Hydroalcoholic extract of *E. uniflora* ripe fruit, EOL = Essential oil of *E. uniflora L.* leaves, EUS = *E. uniflora* seeds.

Table 5 Anti-proliferative effects of *E. uniflora* oils in human cancer cell lines and in human fibroblast cell line.

	Cell lines IC_{50}			
	HCT-116 Colon	AGP-01 Gastric	SKMEL-19 Melanoma	MRC-5 Human Fibroblast
E1	ND	ND	ND	ND
E2 [A]	16.26 (14.45–18.29)	12.60 (10.35–15.35)	12.20 (10.10–14.72)	10.27 (8.15–12.94)
E3 [A]	> 25	> 25	> 25	> 25
E4 [A]	9.28 (7.86–10.97)	8.73 (5.45–13.98)	15.42 (9.38–25.33)	14.95 (9.44–13.90)
E5 [A]	> 25	> 25	> 25	> 25
Curzerene [B]	9.18 (8.18–10.30)	8.04 (5.66–11.41)	5.17 (4.04–6.62)	11.45 (9.44–13.90)

The oils of five specimens (E1 to E5) that occur in the Brazilian Amazon were tested. Data are presented as IC_{50} values and 95% confidence intervals obtained by nonlinear regression for all cell lines, from three independent experiments. *ND = not determined, adapted from Figueiredo et al. 2019. Data are expressed as [A] μg/mL and [B] μM.

1.5 μg.mL^{-1} and *Bacillus subtilis, Streptococcus* spp. and *Escherichia coli* at 16.5 μg.mL^{-1}. This effect can be explained by a channel formation in the membrane cells, which affects cell permeability and leads to cell death (Table 4) (Oliveira et al., 2008) (see Table 5).

4.2. Antifungal activity

Candida spp. is the primary fungal pathogenic agent in humans. Despite belonging to the human microbiota, alteration in tissues in association with virulence factors allow this fungus to invade patients with lower immunologic resistance that are mostly affected. It was demonstrated that *E. uniflora* leaf extract could reduce biofilm formation in cells isolated from the oral cavity in transplanted patients. Various *Candida* fungal strains were evaluated such as *C. tropicalis, C. parapsilosis, C. glabrata, C. orthopsilosis, C. metapsilosis,* and *C. dubliniensis*. A study showed that pitanga could reduce adherence of human oral epithelial cells to the biofilm formation and alter the hydrophobicity of the cell surface of *Candida albicans*, suggesting that the antifungal effect of *E. uniflora* is due to gallic acid and myricitrin, phytochemicals that can act against *Candida spp per se* (Souza et al., 2018).

Another study on *E. uniflora* essential oil also demonstrated antifungal activity against *Candida spp*. When this oil was administered associated with the antifungal fluconazole, the authors did not observe a synergic effect. In fact, this combination compromised the effect of the drugs, whereas the isolated use of the plant or the antifungal were effective. Despite the incompatibility with fluconazole, antifungal effect of *E. uniflora* essential oil were attributed to interference with virulence factors of candidiasis and morphological changes caused through the formation of filamentary structures (Dos Santos et al., 2018). However, when the ethanolic extract was associated with the antifungal drug metronidazole, a combined effect against *C. tropicalis* was found; however, this synergic activity was not evidenced in other strains (Santos et al., 2013). Another virulence factor of *Candida* spp. is the secretion of hydrolytic enzymes which can be reduced by leaf extract from *E. uniflora* (Silva-Rocha et al., 2015).

Besides fungus that colonize the oral cavity, there are those that affect the skin and are responsible for dermatitis. Among these organisms is *Paracoccidioides brasiliensis*, the main organism responsible for systemic mycosis in Latin America. Essential oil from *E. uniflora* was able to inhibit the fungus growth at a concentration of 62.5 μg.mL^{-1}. This effect can be attributed to the presence of selinatrienone derivatives and curzerene compounds in this oil (Costa et al., 2010).

The studies describe the inhibitory effect of *E. uniflora* against biofilm formation and fungal growth. The presence of some compounds in the pitanga extract, such as oleic acid, can be responsible for this response. Muthamil and collaborators (2020) found that this compound is able to reduce the filament formation, induce alterations in ergosterol present in the cell membrane of *Candida spp*. In addition, the acid oleic affects the expression of genes (*asl-1, sap2, hwp1* and *cst20)* involved in the virulence response of *Candida spp*. The flavonols myricetin and quercetin, also present in this fruit, present effect in the biofilm formation of *P. aeruginosa* that acts on the phenazines, a molecules involved in the intracellular redox state and colony biofilm formation, promoting alterations in the electron transporter of this molecules (Pruteanu et al., 2020).

4.3. Antiparasitic activity

Parasitic diseases are significant and neglected health problems in emerging countries and can affect both humans and animals. Social and cultural factors are related to the parasite infections in humans caused by inadequate and unsanitary conditions. Antiparasitic drugs can be quite toxic and thus the search for natural products has been increasing (Wink 2012). Therefore, antiparasitic properties of native plants are particularly interesting for the population of less developed countries.

The essential oil from pitangueira leaves demonstrated antiparasitic activity (IC_{50} 6.10 ± 1.80 μg·mL^{-1}) against *Leishmania amazonensis* (*L. amazonensis)*, which indicates a higher efficacy than the drug pentamidine isethionate (IC_{50} 23.22 ± 9.04 μg·mL^{-1}). This oil is rich in sesquiterpenes, which causes alterations in the mitochondrial and plasmatic membrane of the parasite (Kauffmann et al., 2017). The *Leishmania* genus affects various regions worldwide. In the Americas, the phlebotomus of the genus *Lutzomyia* is the vector. The manifestations of Leishmaniasis include cutaneous sores (localized and disseminated), muco-cutaneous, and visceral ulcers or kala-azar (Torres-Guerrero et al., 2017).

Another study with *L. amazonensis* showed that *E. uniflora* essential oil caused 100% inhibition of promastigotes at the concentrations of 400, 200, and 100 μg·mL^{-1} after 72 h of exposure with an IC_{50} of 1.75 μg·mL^{-1}. As the parasite infects macrophages, a study evaluated the oil's effect in the cells infected with *L. amazonensis*. Pitanga essential essential oil was able to reduce parasite infection due to greater activation of macrophages, with increased phagocytosis capacity and lysosomal activity. It is believed that the terpene compounds act in the isoprenoid pathway, inhibiting one of the stages of ubiquinone biosynthesis, which is required for the advance of the parasite stages. This might explain the anti-*Leishmania* activity of this plant. The lipophilic constituents of essential oils derived these from plants can alter the constitution of cell barriers and lipids of the plasma membrane of the parasitic promastigote stage, leading to the release of cell contents and consequently the inhibition of cytoplasmic processes (Rodrigues et al., 2013).

Similar to *Leishmania*, *Trypanosoma cruzi* is transmitted by an insect, by blood transfusion, organ transplant or ingestion of contaminated food. The recovery rate following medicine treatment is high only in the acute phase of this disease and is less than 20% effective in the chronic phase. However, the drugs available for the treatment are highly toxic. Therefore, it is necessary to search for new alternatives with antiparasitic activity and safety. A study with the epimastigote form, found in the vector of this disease, showed that the pitanga leaf extract could inhibit 80% of the parasite at the concentration of 100 μg·mL^{-1}. This extract also showed low cytotoxic activity in J774 macrophage cells. Only 8% of the cells exposed to a concentration of 100 μg·mL^{-1} of the extract were unviable, and this toxicity was reduced to 0% with a concentration of 10 100 μg·mL^{-1}. These results indicate that *E. uniflora* has

anti-epimastigote potential and locytotoxicity (Costa et al., 2010).

The efficacy of the plant was evaluated also against other parasites of the genus *Trypanosoma* (*T. brucei*), responsible for anemia and damages to organs, such as liver and kidney. The leaves of *E. uniflora* demonstrated effectiveness against trypanosomal infection and the symptoms of this condition, such as anemia. The enzyme adenosine kinase (TbAK) was a target of the plant action (Abdelfattah et al., 2021). In addition, de Souza et al., (2017), demonstrated that components such as tannins and flavonoids of *E. uniflora* fractions are able to protect against the promastigote and amastigote forms of *Leishmania* spp.

Another study evaluated the effectiveness of the extract obtained from the *E. uniflora* leaves against the parasite *Trichomonas gallinae*, which is responsible for trichomoniasis that affects birds. However, the methanolic extract did not yield promising results when compared to the control drug metronidazole. When the $CHCl_3$ and EtOAc fractions of this extract were obtained and tested, an anti-parasitic potential similar to the drug was found (Ibikunle et al., 2011).

The anthelmintic activity depicted by *E. uniflora* extracts has been attributed to the presence of compounds with proven anthelmintic action, such as flavonoids, saponins, tannins and triterpenes. Different extracts of *E. uniflora* inhibited the hatchability of eggs of gastrointestinal sheep nematodes, with a percentage of inhibition ranging from 14.56 to 99.75%. The hydroalcoholic extracts were the most promising compared to the aqueous ones. The chemical composition was analyzed using qualitative phytochemical protocols to observe compounds with proven anthelmintic action, such as flavonoids, saponins, tannins and triterpenes. Thus, the results of study revealed that *E. uniflora* extracts were promising anthelmintic candidates (Castro et al., 2019).

4.4. Antiviral activity

Viruses are unicellular microorganisms that infect cells for survival, triggering an immunological response. For instance, the human immunodeficiency virus (HIV) causes immune system impairment by causing the death of cells involved in the defense mechanism. In this example, the continuous use of retroviral therapy is necessary to reduce the viral load. Notably, some plants can inhibit or reduce viral replication through different mechanisms (Mukhtar et al., 2008) which is the case of *E. uniflora*.

For instance, when tested against the Dengue Virus Serotype 2 in culture human cells (Huh7-it), *E. uniflora* leaf extract showed antiviral activity with an IC_{50} of 19.83 $\mu g.mL^{-1}$ (Dewi et al., 2019). It has been described that some flavonoids can inhibit the protease enzymes involved in viral replication (Qamar et al., 2017). For HIV treatment, the use of antiretroviral therapy presents efficacy but causes some side effects associated with the need for continuous administration. Notably, the methanolic and water extracts from *E. uniflora* leaves showed a replication inhibition at 100 $ug.mL^{-1}$ (94%) against HIV-1, promoting the inhibition of the protease required in replication and viral action (Kawahata et al., 1996).

Some viruses have long latency periods, therefore they activate during some immunocompromising condition. The Epstein-Barr virus (EBV) is one such virus, causing a condition known as herpes and mononucleosis. Its viral mechanism is associated with the presence of DNA polymerase enzyme that favors replication. The tannins isolated from *E. uniflora* leaf extract, Eugeniflorin D1 and D2, were found to have inhibitory effect against this virus at concentrations of 3.0 and 3.5 μM, respectively; the mechanism by which they conferred this effect was by blocking the DNA polymerase enzyme (Lee et al., 2000).

4.5. Anti-inflammatory effect

The anti-inflammatory capacity of *E. uniflora* extract has shown promising results as demonstrated by Bello et al. (2020) who used the ethanolic extract of the leaves in a model of acute formalin-induced inflammation in rats. In this study, the effects of *E. uniflora* at doses of 50, 100 and 200 $mg.kg^{-1}$ were similar to those of ibuprofen (100 $mg.kg^{-1}$, p.o), a standard non-steroidal anti-inflammatory drug (NSAID). This demonstrates the high effectiveness of ethanolic extract against inflammatory processes caused by acute injury. Additionally, the ethanolic extract was able to limit the area of secondary damage in the tissue and to accelerate the recovery of the soft tissue after the injury, leading to the reduction of inflammatory cells in the injured hind paw.

In a different experiment, Falcão et al. (2018) treated carrageenan-induced peritonitis in rats with crude extract, aqueous fraction (AqF) or EAF from *E. uniflora* leaves. They observed anti-inflammatory properties with reduced levels of IL-1β (Interleukin-1 Beta) following treatment with the crude extract in both fractions and at all doses used (50, 100 and 200 $mg.kg^{-1}$). Remarkably, the aqueous fraction also stood out due to the decrease in TNF-α (Tumor Necrosis Factor-Alpha) levels. In addition, the anti-inflammatory effect of the extracts and their fractions also showed the reduction of lipid peroxidation that occurred during treatment. This implies that the antioxidant effect would be mediated by an intracellular reduction in glutathione (GSH) consumption, which would cause, in part, increase in the anti-inflammatory potential.

Similarly, *E. uniflora* leaf extracts (aqueous, ethanolic and essential oil) were assessed by Schapoval et al. (1994). Using the carrageenan-induced rat paw edema test, the authors found that the ethanolic extract (300 $mg.kg^{-1}$, v.o) was more effective than the aqueous one, which was attributed to the presence of volatile or unstable substances that underwent changes during the time necessary for drying and/or extraction even at room temperature. Using a similar protocol of carrageenan-induced hind-paw edema, Sobeh et al. (2019) found that the methanolic extract from *E. uniflora* leaves decreased the thickness of the edema and reduced leukocyte migration to the peritoneal cavity. Furthermore, it was demonstrated for the first time that the extract inhibits cyclooxygenases (COX-1 and COX-2) and lipoxygenase (LOX) therefore reducing the production of pro-inflammatory mediators. Although the extract showed greater selectivity for COX-2, its LOX inhibitory activity was similar to that of the diclofenac.

Furthermore, Syama et al. (2019) demonstrated that the leaf ethanolic extract showed an important action in cell line RAW264.7 stimulated by lipopolysaccharide (LPS). The study revealed the extract's ability to inhibit enzymes that regulate inflammation, which was also confirmed by decrease in the

expression of COX-2 and nuclear factor-kB (NF-kB). *In vivo* carrageenan-induced chronic inflammatory studies in male Wistar rats demonstrated that doses of 250 and 500 mg.kg^{-1} ethanolic extract of leaves decreased the inflammatory response possibly through the inhibition of pro-inflammatory mediators. This could be attributed to the presence of gallic acid and dihydromyricetin that have proven anti-inflammatory property.

There are reports of *E. uniflora*'s influence in reducing infection induced by *Helicobacter pylori,* a bacteria that causes gastric ulcerative disorders that in more severe cases can develop into gastric cancer. Monteiro et al. (2019) demonstrated that leaf *E. uniflora* methanolic extract decreased inflammatory activity through the use of murine macrophage cell culture RAW 264.7 (ATCC TIB-71) stimulated by LPS. The results demonstrated a reduction in IL-6, TNF-α and nitric oxide (NO) levels at all concentrations tested. However, the concentration 100 μg.mL^{-1} reached the highest inhibition rate of about 83.19, 39.10 and 97.20%, respectively.

The anti-inflammatory potential of *E. uniflora* purple pulp juice has also been reported in gingival epithelial cells. It acts by attenuating the release of IL-8 (Interleukin-8) in non-stimulated and prostaglandin-*LPS*-stimulated cells, respectively (Soares 2014). In addition, important constituents present in the juice such as cyanidin-3-glucoside and oxidoselina-1,3,7(11)-trien-8-one were able to reduce CXCL8 mRNA expression by HGF-1 cells and IL-8 release, thereby revealing an anti-inflammatory potential of the volatile compound oxidoselina-1,3,7(11)-trien-8-one, reported for the first time in the literature.

Another study conducted by Schumacher et al. (2015) reported that the anti-inflammatory effects of *E. uniflora* leaf extract also contributed to improvement in type 1 diabetes mellitus induced in non-obese rats. Parameters such as decreased inflammatory cell infiltration associated with attenuating oxidative stress, increased levels of hepatic GSH and seric insulin indicate that these associated effects could help preserve insulin-producing pancreatic ß cells and inflammatory insult. However, the authors stated that a better explanation regarding the anti-inflammatory signaling process of the immune response is required.

In addition, the anti-inflammatory effects of these leaves were also confirmed using the Cecal Ligation and Puncture model in mice. The results indicated that 150 and 300 mg.kg^{-1} doses given orally 1 h before surgery and 6 h after the procedure managed to significantly decrease serum levels of TNF-α by 36.6–38.8%, and levels of IL −1β were also inhibited by 32.3–38.5% after 6 h of induction in the false surgical group. Another important product of cell inflammation was the decrease in induced nitric oxide synthase (iNOS) levels by septic mice ileum cells as *E. uniflora's* aqueous extract at all doses (75, 150 and 300 mg.kg^{-1}) decreased iNOS levels by 35.2, 33.6 and 75.2%, respectively. Furthermore, COX-2 expression was reduced by 12.7 and 62% after treatment with higher doses (Rattmann et al., 2012).

4.6. Anti-cancer activity

Anti-cancer activity is based on the cytotoxic potential of a molecule. As previously mentioned, *E. uniflora* extracts do not cause significant toxicity, especially when the organism or cells are healthy. However, tumorous cells present different membrane and metabolic characteristics, proliferating under oxidative stress and impaired antioxidant defense (Fry and Jacob 2006). Then, it is possible that altering redox status may trigger apoptotic cell death in carcinogenic cells. Therefore, several promising results have been described in this field.

Nuñez et al. (2018) demonstrated that the aqueous leaf extract of *E. uniflora* showed positive results in a human tumorous cell line derived from invasive cervical carcinoma, SiHa (HPV 16-positive). The data demonstrated that all concentrations of *E. uniflora* extract (0.5–20 mg.mL^{-1}) significantly inhibited the viability of the SiHa cell line in 24 h and 48 h, and this effect was prolonged at the highest doses of 10 mg.mL^{-1} 72 h after treatment. In addition, the migration of tumor cells significantly reduced after 24 h of treatment to 63.4% and in 48 h to 24.5%, and the capacity of tumor cell adhesion decreased in a dose-dependent manner (5, 10 and 20 mg.mL^{-1}). In this case, cell death due to apoptosis was also observed in tumor cells treated with *E. uniflor*a and mitigation of the migration, adhesion, colony formation and recovery capacities was observed even after treatment withdrawal without altering the normal cells viability.

Promising results of using *E. uniflora* against carcinogenic activity were found by Ismiyati et al. (2012) in the breast cancer T47D cell line treated with the extract obtained from the leaves. The results demonstrated an antiproliferative effect at 50 μg.mL^{-1} 48 h and 72 h hours after incubation. At 75 μg.mL^{-1}, the extract decreased cell proliferation during the entire incubation period (24 h, 48 h and 72 h). Additionally, a cytotoxic effect was also observed, which may have contributed to inhibiting the proliferation of T47D cells and inducing apoptosis.

The cancer cell lines HCT-116 (colon), AGP-01 (malignant gastric ascites) and SKMEL-19 (melanoma) were treated with different *E. uniflora* leaf oils in a study by Figueiredo et al. (2019). Despite the variations between oils, their constituents had common predominance and belonged to the classes of oxygenated sesquiterpenes (20.8–69.0%) and sesquiterpene hydrocarbons (18.0–53.9%). Figueiredo et al. (2019) demonstrated that curzerene, selin-1,3,7(11)-trien-8-one and selin-1,3,7(11)-trien-8-one epoxide were found in oil extract and all stood out as potential anti-cancer agents for lung, colon, stomach and melanoma tumors. Cytotoxic activity was demonstrated by the two types of oil against all tested HCT-116 cell lines. In addition, curzerene showed the most significant activity against melanoma cells (SKMEL-19), induced apoptosis at 5.0 and 10.0 μM compared to vehicle DMSO and exhibited a decrease in cell migration at 5.0 and 10.0 μM after 30 h of treatment.

Another study using MCF-7 cells (breast cancer cell line) demonstrated that *E. uniflora* essential oil presented an IC_{50} of 11.20 μg.mL^{-1} and a selectivity index of 6.82, making it an interesting candidate for further studies in terms of anti-carcinogenic properties. In this study, *E. uniflora* oil presented more than 80 compounds, the most predominant of which were from the oxygenated sesquiterpenes class known as spathulenol (15.8%), α-copaene (10.96%), muurola-4,10-dien-1-β-ol (9.3%), caryophyllene oxide (8.93%), alloaromadendrene (5.5%) and nootkatone (5.17%) (Sobeh et al., 2016).

Finally, Ogunwande at al. (2005) used essential oil extracted from fully grown leaves and fruit and found effects

on tumor cells of the human prostate (PC-3), liver (Hep G2) and breast (Hs 578 T). The results identified mostly sesquiterpenoid compounds in both oils. In the leaves, the compounds identified were curzerene (19.7%), selina-1,3,7 (11)-trien-8-one (17.8%), atractylone (16.9%) and furanodiene (9.6%), and those from the fruits were germacrone (27.5%), selina-1,3,7(11)-trien-8-one (19.2%), curzerene (11.3%) and oxidoselina-1,3,7(11)-trien- 8-one (11.0%). In this case, the volatile oils exhibited an excellent cytotoxic action in relation to the human cell lines of PC-3 (99.36% and 99.55%) and Hep G2 (99.71% and 99.96%), while completely inhibiting the growth of Hs 578 (100%) by percentage of fruit and leaf oil, respectively.

4.7. Neuroprotective effect

Studies evaluating *E. uniflora*'s neuroprotective potential are still relatively scarce. Da Da Silva et al. (2019) used the ethanol extract of *E. uniflora* leaves to observe its neuroprotective effect on memory impairment induced by intracerebroventricular injection of streptozotocin (STZ, i.c.v) in rats. The administration of STZ in rats is a model of sporadic Alzheimer's disease widely accepted for inducing impairment in memory and metabolic changes similar to those of patients. Therefore, rats that received leaf *E. uniflora* extract at doses of 300 and 1000 mg.kg^{-1} for 30 days alternately, after i.c.v administration of STZ, demonstrated improvement in episodic memory and learning compared to the untreated animals. Additionally, the performance of the animals that received the extracts were better than untreated animals in both doses tested. The neuroprotective effects have been attributed to the antioxidant and anti-inflammatory properties that have also been described in previous studies using other species of the genus *Eugenia*. In this case, this study was the first to report potential neuroprotective effects of pitangueira leaves in this neurodegenerative disease model.

The antioxidant and anti-acetylcholinesterase actions of red pitanga extract chronically administered at a dose of 200 mg/kg was analyzed in male Swiss mice in a model of depression. Flores et al (2020) observed promising results regarding the prevention of the depressive effect induced by unpredictable chronic stress, provided by the regulation of acetylcholinesterase activity, reducing the production of reactive oxygen species in the prefrontal cortex and hippocampus and avoiding glutathione peroxidase in the hippocampus of treated animals. It is important to emphasize that the administration of the extract of the red pitanga produced neuroprotection similar to the classic antidepressant fluoxetine, which was used as a positive control. Therefore, these findings may suggest a potential role for the *E. uniflora* in the treatment of depressive disorders.

Neuroprotective effects of red and purple pulp extracts of *E. uniflora* were observed in models of Alzheimer's and Parkinson's diseases induced by amyloid β peptide fragment 1–42 (a$\beta_{1\text{-}42}$) and MPP+, respectively, in *C. elegans*. Borges et al. (2015) demonstrated that the effects induced by a$\beta_{1\text{-}42}$ were reduced in animals treated with both extracts. These could reduce the paralysis phenotype in *C. elegans*. The authors highlighted that purple pitanga extract presented a higher efficacy than red pitanga extract. Additionally, they also favored important genes of oxidative and thermal stress activation such as the transcription factors daf-16 and Nrf2/Skn-1/ inhibition pathways. In the neurodegeneration induced by MPP+, both red and purple pitanga extracts could reduce paralysis in *C. elegans*, but the red pitanga extract presented the highest percentages of reduction compared to the control.

Based on the data presented, *E. uniflora* is a promising natural product for the development of new drugs aiming at the central nervous system. The presence of anthocyanins, of which cyanidin-3-O-glucoside is the main compound present in pitanga, demonstrates the neuroprotective mechanism against the formation of free radicals and oxidative processes in the body, since these endogenous processes are related to the genesis of several neurodegenerative diseases.

However, a better understanding of the mechanism of action of the majority compounds such as flavonoids, terpenes and phenolic compounds is still needed, therefore, in addition to components for the development of new drugs, they can become a form of complementary treatment through the diet.

4.8. Antioxidant effect of Eugenia uniflora

Exogenous food antioxidants such as polyphenols and carotenoids can help to protect an organism against diseases associated with oxidative stress (Rahimi-Madiseh et al., 2017). Antioxidant activity of the chemical compound (s) or extract (s) vary according to the model used and also according to the ability of the phytochemical (da Cunha et al., 2016). Currently, several studies have investigated the antioxidant capacities of *E. uniflora* using *in vitro* and *in vivo* assays particularly because this potential might be responsible for several biological advantages attributed to *E. uniflora*.

4.8.1. In vitro antioxidant activity

An *in vitro* study performed on human keratinocyte cells (HaCaT cell) evaluated the protective activity of *E. uniflora* against oxidative stress induced by UVA irradiation (100 J. cm^{-2}). The cells were pre-treated with 50 μg.mL^{-1} of methanolic extract obtained from leaves. High levels of reactive oxygen species (ROS) and p38 activation (mitogen-activated protein kinases) were found to have been reduced with concomitant increase in GSH levels compared to stressed cells. This protective response can be associated with the presence of total phenols in the *E. uniflora* extract, which have strong antioxidant capabilities (Sobeh et al., 2019).

Similarly, several studies have demonstrated the free radical scavenging activity of different *E. uniflora* extracts. The leaf extract has a high content of flavonoids (42.46 mg.g^{-1}) and showed a sequestering DPPH radical activity with an EC_{50} 185.47 μg.mL^{-1}. The extract also reduced the levels of lipid peroxidation (levels of reactive substances) in the TBARS assay to the baseline when induced with Fe^{2+} (Sobral-Souza et al., 2014). In another study, the leaf hydroalcoholic extract presented an EC_{50} of 14.19 μg.mL^{-1} in DPPH assay and 19.75 μg.mL^{-1} in the ABTS radical scavenger test. The results obtained with the TBARS *in vivo* tests and levels of advanced oxidation protein products (AOPP) demonstrate that treatment for four weeks with this extract reduced oxidative stress in the plasma of treated rats compared to the control group, highlighting the antioxidant activity of the extract (Peixoto et al., 2019).

In a study conducted with four native Brazilian fruits, the purple pitanga extract was found to have the highest DPPH

radical scavenger activity and also presented the highest FRAP (Fe-reducing antioxidant potential) followed by orange and red pulp seed extracts. These results were attributed to the antioxidant capacity of compounds such as quercetin, quercitrin, isoquercitrin and cyanidin derivatives (Denardin et al., 2015).

The leaf ethanolic extract (1–480 mg.mL^{-1}) inhibited Fe^{2+}-induced lipid peroxidation in rat brain and liver homogenates and eliminated the DPPH radical. Notably, this extract further presented a high content of some polyphenolic compounds such as quercetin, quercitrin, isoquercitrin, luteolin and ellagic acid, which might be at least partly responsible for its antioxidant effect (da Cunha et al., 2016).

The antioxidant compounds isolated from *E. uniflora* such as cyanidin-3-glycoside and delfinidin-3 glycoside are highly unstable and require technology to protect them from degradation. Microencapsulation is a technology used to protect active ingredients. Therefore, spray drying was used to evaluate High-performance Agave Frutans (HPAF) and High Degree of Polymerisation Agave Fructans (HDPAF) and maltodextrin (MD) as coating materials, respectively. The results showed that the highest yield and concentration of anthocyanins after drying and during storage were found at a ratio of 1:6 core: wall material. This study showed that the fraction of both fructans had encapsulation properties similar to that of MD. Moreover, HDPAF was more effective than MD in protecting antioxidants during drying and storage, and the total color change could be used as an indicator of anthocyanin degradation during storage (Ortiz-Basurto et al., 2017).

4.8.2. In vivo antioxidant activity

In an experimental model of insulin resistance induced by DEX (dexamethasone), 200 mg.kg^{-1}.day^{-1} of *E. uniflora* fruit extract was administered for 21 days. The extract was able to prevent lipid peroxidation and the formation of ROS in rat liver, suggesting its important antioxidant action in the experimental model (de Souza Cardoso et al., 2018). Additionally, Schumacher et al (2015), found that repeated consumption of aqueous leaf extract in a type 1 diabetes mellitus model in mice showed reduction in the rate of inflammatory infiltrate in pancreatic islets, with serum levels of insulin and hepatic GSH being maintained and seric lipid peroxidation and the risk of diabetes being reduced.

To better understand the effects of the fruit on aging and conditions related to oxidative stress, the ethanolic extract of the purple *E. uniflora* fruit pulp was tested in the alternative model *C. elegans*. Exposure to the extract showed improvement in survival after different situations of oxidative stress and was also seen to prolong the lifespan of N2 (wild type) and *mev-1* mutants, increasing the expression of SOD-3 and HSP-16.2 and the nuclear localization of DAF-16, which are alterations that promoted longevity by modulating antioxidant signaling (Tambara et al., 2018).

A study investigated the antioxidant effect of ethanolic sun-dried (PCS) and air-dried (PCA) extracts from *E. uniflora* leaves in rat brain and liver. The results indicated that while air-dried leaves significantly inhibited the formation of TBARS in liver and brain tissue homogenates, PCS did not. Subsequent investigations revealed that the phenolic content of PCS was significantly lower compared to PCA, thereby suggesting that air-drying should be used in the preparation of the extract as phenolics significantly contribute to the plant's antioxidant potential (Kade et al., 2008).

Meira et al., (2020) evaluated the antioxidant effects of the hydroalcoholic extract of *E. uniflora* leaves at the dose (200 mg / kg, p.o) in Wistar rats, 28 days before the induction of acute kidney injury (AKI) by bilateral renal ischemia for 45 min. Renal production of reactive oxygen species and apoptosis, SOD and catalase expression and activity were determined. Treatment with pitanga prevented the AKI-induced decrease in glomerular filtration rate and renal blood flow, as well as the increase in renal vascular resistance. The *E. uniflora* extract also prevented the increase in oxidative stress and apoptosis, probably due to the increased activity and expression of antioxidant enzymes. These results demonstrate a protective effect of pitanga extract on the development of AKI. This protective effect of *E. uniflora* extract on oxidative stress can be attributed to identified compounds, such as flavonoids, polyphenols and terpenes. These substances are able to reduce oxidative stress through similar mechanisms, such as increased SOD activity, catalase and glutathione peroxidase.

The active edible coatings and films produced by the addition of plant extracts and antimicrobial compounds are of interest to food packaging. In this sense, Chakravartula et al., (2020) sought to develop and characterize a film and film forming solution based on mixtures of cassava starch/chitosan (CS/CH) incorporated with cherry tree leaf extract of *E. uniflora L* (PE) and/or natamycin (NA) and studies their effects on selected physical properties, antioxidant and antifungal activity. The addition of PE did not affect the mechanical properties of the film, while NA significantly decreased the flexibility of the films due to changes in the behavior of the parafragile ductile biopolymer. Structural analysis by FTIR and XRD indicated interaction between the components, particularly the presence of new vibration peaks C]O and change in wavenumbers of the characteristic CS/CH mixture. The antioxidant activity of the films significantly increased with PE, although the combination of additives resulted in reduction of activity. Positive antifungal effect of films containing NA was observed against *Aspergillus flavus* and *Aspergillus parasiticus*, indicating potential for applications in active food packaging.

These promising data on antioxidant effects both *in vitro* and *in vivo* can be related to the accumulation of phenolic compounds such as anthocyanins present in *E. uniflora* extract as well as in leaves, which corroborates to the phytochemical characterization already described in this review.

4.9. E. uniflora effects on metabolism and TGI

E. uniflora leaves are rich in tannins and flavonoids (Auricchio and Bacchi 2003) and several studies have shown that tannin-rich species have been traditionally used for their gastroprotective properties (de Jesus et al., 2012). In fact, Souza and Costa (2017) demonstrated the gastroprotective effect of an aqueous fraction of hydroacetonic leaf extract of *E. uniflora* against several gastric ulcer models in mice; increase in the gastric mucus and reduced GSH levels were also found.

Gastric mucus is the first line of defense of the gastric mucosa. It is a transparent, viscous, elastic adherent gel made up of water and glycoproteins (Martins et al., 2015). The mucus layer is a physical barrier that adheres with bicarbonate

and protects the underlying mucosa from proteolytic digestion (Allen and Flemstrom 2005). Furthermore, it is known that NO is crucial in the defense of the gastric mucosa and is a biological mediator which regulates the secretion of mucus and blood flow (Falcao Hde et al., 2013). Souza and Costa (2018) demonstrated that an inhibition of NO synthase by L-NAME did not reverse the gastroprotection effect of the aqueous fraction of hydroacetonic leaf extract of *E. uniflora,* suggesting that NO synthesis is not critical to its gastroprotective activity. Thus, it seems that the primary mechanism of the action of leaf extract of *E. uniflora* is through increased gastric mucus.

In 2008, a hepatoprotective effect of leaves of *E. uniflora* against lipid peroxidation was demonstrated *in vitro*. This can be attributed to the antioxidant properties of *E. uniflora* extract (Kade et al., 2008). Another study conducted by Fiuza et al. (2009) showed a hepatopancreas action of crude ethanol extract and fractions in *Oreochromis niloticus L.* Recently, Sobeh et al. (2020) showed that the polyphenol-rich fraction from *E. uniflora* leaves has substantial hepatoprotective activities against acute liver injury in rats due to its antioxidant property.

Furthermore, a hypotensive activity in normotensive rats has been demonstrated following administration of 3 mg. kg^{-1} of dried leaves of a crude aqueous extract. This effect was associated with a direct vasodilating action in perfused resistance vessels and a slight diuresis at higher doses (120 mg dried leaves.kg^{-1}) (Consolini et al., 1999, Consolini and Sarubbio 2002). Additionally, a cardiovascular activity caused by aqueous crude extract (ACE) of *E. uniflora* was demonstrated in rats through β-adrenergic mechanisms. In this case, the release of catecholamines and Ca-blocking action might have produced this therapeutic effect (hypotension) and contributed to chronotropic and inotropic effects on the heart (Consolini and Sarubbio 2002).

In relation to metabolism, folk medicine reports the use of hydro-alcoholic extract of *E. uniflora* leaves to control the levels of triglycerides, very low-density lipoprotein (VLDL) cholesterol and uric acid in *Cebus paella,* monkeys (Ferro et al., 1988). Furthermore, Arai et al. (1999) showed that extracts from the leaves of *E. uniflora* had improved effects on postprandial hyperglycemia and hypertriglyceridemia, and these effects can be attributed to the inhibition of sugar and fat decomposition and reduction of glucose absorption. The red variety of *E. uniflora* fruit demonstrated effects against high levels of glucose, triacylglycerol, cholesterol and LDL cholesterol, as well as visceral fat and weight accumulation (Oliveira et al., 2017).

Additionally, Schumacher et al. (2015) studied the effects of continuous treatment with aqueous extract of dried leaves of *E. uniflora* in an experimental model of spontaneous type 1 diabetes mice. This treatment was found to reduce the incidence of type 1 diabetes, decreasing inflammatory cell infiltration and the oxidative stress and increasing hepatic GSH levels and serum insulin. This may indicate preservation of insulin-producing pancreatic β cells.

Another interesting effect was observed with respect to α-glucosidase activity. Even at low concentrations, the ethanolic extract of purple *E. uniflora* leaves inhibited almost 100% the activity of the aforementioned enzyme (IC_{50} 0.26 $\mu g.mL^{-1}$) (Vinholes and Vizzotto 2017). The *E. uniflora* fruit juice was also found to inhibit α-glucosidase activity in 69.47 ± 2.89 % at 1 $mg.mL^{-1}$. The total phenolic content of the juice was 367.00 ± 11.42 mg $GAE.L^{-1}$ and was considered important to the inhibitory activity observed in the study (Siebert et al., 2020).

This inhibitory effect can be associated with the presence of fatty acids and derivatives. Unsaturated fatty acids such as oleic, linoleic, and linolenic acids and their methyl ester forms inhibit α-glucosidase enzyme through competitive mode inhibition (Su et al., 2013). Furthermore, phenolic compounds such as salicylic acid derivatives showed interaction with α-glucosidase enzyme (Chen et al., 2019). Therefore, the inhibitory properties of the ethanolic extract show promising results as the inhibition of this digestive enzyme is used to control type 2 diabetes mellitus.

Furthermore, *E. uniflora* fruit (red variety) standardized extract has a beneficial effect in rats submitted to metabolic syndrome induced by diet. This extract presented an antihyperglycemic, antihyperlipidemic and a neuroprotective role as it presented antioxidant and antidepressant-like effects (Oliveira et al., 2018). Moreover, liposomes loaded with an ethanolic extract of purple pitanga were found to reduce lipid accumulation induced by high cholesterol levels in *C. elegans* (Roncato et al., 2019).

It is evident that *in vitro* and *in vivo* studies prove that bioactive compounds present in pitanga can positively affect metabolism biomarkers. The mechanism of action against diabetes have been attributed to the phytochemicals and include modulation of carbohydrate metabolism, glucose homeostasis and insulin secretion, reducing oxidative stress, suppressing the formation of advanced glycation end products and protecting / regenerating pancreatic β-cells. Therefore, leaves and the fruits of *E. uniflora* have been showing therapeutic potential to be used in the treatment of diabetes and its comorbidities.

These results are interesting as they again point out that natural antimicrobial and antioxidant compounds have shown potential application for the production of active packaging and meet the growing demand from consumers, who are increasingly looking for food products with the lowest amount of artificial additives.

5. Majority compounds *E. uniflora* - possible mechanisms

As described in this review, several biological properties have been attributed to leaf, fuit and seeds extracts obtained from *E. uniflora* (Fig. 3). Some studies explored even further by investigating which components were responsible by these pharmacological effects and how they act in molecular targets. For instance, it has been demonstrated that pure phenolics delphinidin 3-O-glucoside and cyanidin-3-O-glucoside inhibit the viability of human colon cancer cells, HCT 116 and HT-29 by inducing apoptosis (Mazewski et al., 2019). These metabolites have shown potential for binding and inhibiting immunological checkpoints, PD-1 and PD-L1, which can activate the immune response in the tumor microenvironment and induce the death of cancer cells. Additionally, the flavonoids also induced apoptosis in the same cancer cell lineage by inhibiting tyrosine kinases (Mazewski et al., 2018).

Antioxidant ad anti-inflammatory actions depend on similar pathways, using cell line RAW 264.7 and inducing inflammatory response with lipopolysaccharide, it was possible to

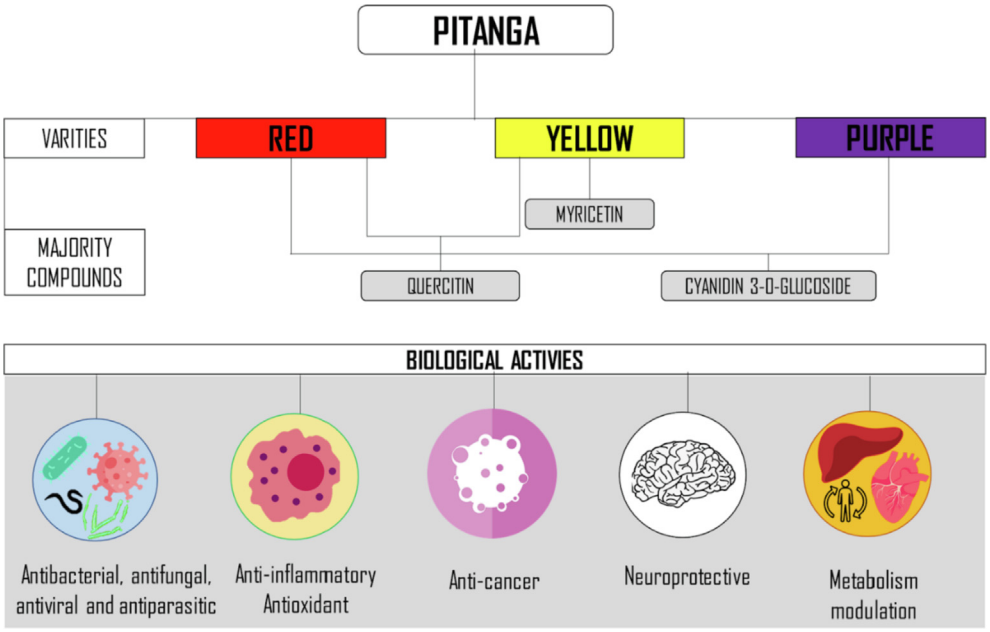

Fig. 3 The major bioactive compounds found in different pitanga varieties and their beneficial effects.

observe that Pelargonidin 3-O-glucoside arrests IkB-α activation and reduces JNK-AMPK phosphorylation, therefore reducing NF-κB signaling (Duarte et al., 2018). Reports demonstrate that myricetin has anti-inflammatory property and can inhibit IL-1β-induced inflammatory mediators in cells. Myricetin was also found to be a potential inhibitor of the COX-2 enzyme (Hiermann et al., 1998, Chen et al., 2001, Rattmann et al., 2012, Li et al., 2013). In *C. elegans* it was possible to observe that myricetin reduced the accumulation of ROS and also the aging pigment lipofuscin by modulating the transcription factor DAF-16, therefore prolonging worms lifespan (Buchter et al., 2013).

According to Lingaraju et al. (2016), kaempferol isolated from the leaf of Eugenia jambolana has anti-inflammatory effects that may be related to the decrease in the level of paw edema in rodents by reducing the activities of NO and MPO. It probably exerts anti-inflammatory effects through the suppression of TNF-α and IL-1β. This reduction in inflammation is also important for hepatoprotective effects that have been attributed to the presence of flavonoid, such as quercetin, myricetin, apigenin and kaempferol glycosides, which have antioxidant activity and had a broad spectrum of bioactivity, according by Sobeh et al. (2020).

A comparative data between majority bioactive compounds, pharmacological action and target tissue is shown in Table 6.

6. Technological potential of *E. uniflora*

In terms of innovation in the food and pharmaceutical areas, *E. uniflora* stands out for its wide application. According to De Araújo et al (2019) it was possible to verify patent applications related to this fruit including extraction processess, beverage preparations and herbal products, just to name a few.

For biological control, botanical insecticides that involve the use of essential oils can be a safe and eco-friendly option for insect control. In a study by Stenger et al., (2021) aiming to minimize productive losses in *Eucalyptus*, an important hardwood tree that is affected by the bronze insect *Thaumastocoris peregrinus*, it was possible to determine the efficacy of *E. uniflora*. In addition, authors described the selectivity of this oil on the parasitoid *C. noackae* and its parasitism in *T. peregrinus*. The essential oil showed insecticidal potential in adults, nymphs and eggs of *T. peregrinus*, and was safer for *C. noacka* when applied one day after parasitism than for pre-parasitism and 7 days after parasitism. The majoritary compounds found in the essential oil of *E. uniflora* were calame-10-one (20.20%), silfiperpherol-6-in-5-one (10.06%) and germacrone (6.61%).

Edible films are thin and flexible materials based on natural biopolymers and have additives generally recognized as safe (GRAS). Biopolymer-based films are biodegradable and, in this sense, they generate interest in replacing or reducing the use of synthetic plastic, which leads to serious problems of ecological accumulation. In this sense, the study by Tessaro et al, (2021), sought to evaluate the effect of incorporating a double emulsion (DE) water-in-oil-in-water (W/O/W) loaded with hydroethanolic extract of pitanga leaf in physicochemical, antimicrobial and antioxidant properties of films based on gelatine, chitosan and gelatine/chitosan mixture to guide the future application of these films as active food packaging. As a result, the incorporation of double emulsion W/O/W to encapsulate pitanga leaf hydroethanolic extract generated films with high antioxidant activity. However, only gelatin-based and DE films inhibited Staphylococcus aureus. The other films containing DE inhibited the growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella ssp* only in the region of contact with the films. The incorporation of pitanga leaf hydroethanolic extract loaded DE affected the physical properties of gelatine, chitosan and gelatine/chitosan films. Overall, DE-added films were more intense in color and had higher roughness but less hydrophobicity and gloss than the controls on the airside surface. In addition, they presented an important barrier to UV/visible light, in addition to greater mechanical strength and stiffness, when

Table 6 Comparative table between majority bioactive compounds, pharmacological action and target tissue.

Majority Bioactive Compounds	Pharmacological activity/tissue	Experimental model	References
Sesquiterpenes compounds	1.1. antibacterial and anti-inflammatory/ Blood cell 1.2. Antibacterial/oral	*1.In vitro* and phase II clinical trial (children)	1. Jovito et al., 2016
	2. Antiparasitic/Cultivation of Leishmania promastigotes	2. *In vitro*	2. Kauffmann et al., 2017
	3. Anti-cancer/Cell culture	*3. In vitro*	3. Figueiredo et al., 2019
delphinidin 3-O-glucoside, cyanidin 3-O-glucoside	1. Antioxidant/brain, liver and kidneys	*1.In vitro* and *in vivo* (mice)	1. Oliveira et al., 2018;
pelargonidin 3-O-glucoside, myricetin, kaempferol, quercetin.	2. Antibacterial and antifungal/oral	*2.In vitro*	2. Thambi et al., 2013; Fiuza et al., 2019; Santo et al., 2013, 2015;Dos Santos et al., 2018;
	3. Antiparasitic/Cultivation of *Trichomonas gallinae*	*3. In vitro*	3. Ibikunle et al., 2011; Santos et al., 2012;
	4.Anti-inflammatory/ Paw	*4. In vitro* and *in vivo* (rats)	4. Bello et al., 2020; Falcão et al., 2018; Apel et al., 2004;
	5. Anti-cancer/Cell culture	*5. In vitro*	5. Núnes et al., 2018;Ismiyati et al. 2012;
	6. Neuroprotective/Brain	*6. In vivo* (rats)	6. Da Silva et al.,2019;Borges et al., 2015;
	7. Cardiovascular activity/ Heart and vessels	7.*In vivo* (rats)	7. Consolini et al., 1999;Consolini et al., 2002;
Gallic acid 3-O-[6′-O-acetyl-β-D-glucoside]	1. Anti-inflammatory, anti-nociceptive, antioxidant and anti-diabetic/central and peripheral	*1. In vivo (mice)*	1. Sobeh et al., 2019
Gallic acid and myricitrin,	1.Antifungical/mycological culture and Human Erythrocytes	*1.In vitro*	1.Souza et al., 2018;
	2. Anti-inflammatory/ Paw and Blood cell	*2. In vivo*	2. Syama et al., 2020
Selinatrienone derivatives and curzerene compounds	1.Antifungical/ mycological culture	*1.In vitro*	1.Costa et al., 2010;
Flavonoids: saponins, tannins and triterpenes	1. Anthelmintic/ Culture	*1. In vitro*	1. Castro et al., 2019;
	2. Antiviral/Culture	*2. In vitro*	2.Qamar et al., 2017; El Mekkawy et al., 2009; Lee et al., 2000;
	3. Antioxidant/*In vitro*	*3. In vitro*	3. Denardin et al., 2015; Peixoto et al., 2018;
	4.Antioxidant/*C.elegans*	*4.In vivo (C.elegans)*	4. Tambara et al., 2018;
	5. Gastroprotective properties/ Gastric mucosa	*5.In vivo (mice)*	5. de Jesus et al., 2012;Eric de Souza & Suzana da Costa, 2017; Falcão et al., 2013;
	6. Antihyperglycemic, antihyperlipidemic action/Blood	*6. Ex vivo (mice)*	6. Oliveira et al., 2017;
	7. Antihyperlipidemic action/*C.elegans*	*7. In vivo (C.elegans)*	7. Roncato et al., 2019;
Gallic acid; rutin and ellagic acid.	1. Anti-inflammatory and antidiabetic	1. *In vitro* and *in vivo (rats)*	1. Schumacher et al. 2015
	2. α-glucosidase activity	*2.Ex vivo (rats)*	2. Vinholes & Vizzotto, 2017;Siebert et al., 2020;
Quercetin, quercitrin, isoquercitrin, luteolin and ellagic acid	1. Antioxidant/ Human blood cells	1. *In vitro*	1. Da Cunha et al. 2016;
Phenolic, flavonoid, and anthocyanin	1. Antioxidant/Liver	1.*In vivo* (rats)	1. De Souza Cardoso et al., 2016;
	2. Hepatoprotective activities/Liver	2.In vivo (rats)	2.Sobeh et al., 2020;
	3. Beneficial action on hepatopancreas/ Liver and pancreas	3. In vivo (fish)	3. Fiuza et al., 2009;
Monoterpenes and sesquiterpenes	1.Metabolic actions/Blood	4. *Ex vivo* (rats);	1.Arai et al., 1999;Ferro et al.,1988;

compared to films without DE. These results demonstrated that the incorporation of the W/O/W emulsion encapsulating the pitanga hydroethanolic extract did not cause any deleterious effect on the properties of the films. The high barrier to UV/Vis light of these films is notable, suggesting an application for protecting lipid-rich foods.

A market that has been growing in recent years is that of functional drinks made from probiotics and kombucha (Kapp and Sumner 2019). Kombucha is a drink made by fermenting tea (usually black tea) and sugar, with a symbiotic culture of bacteria and yeast (SCOBY) which is a biofilm of microorganisms. Kombucha's popularity as a functional food is driven by its alleged health benefits, which include multiple functional properties such as anti-inflammatory potential and antioxidant activity (Martínez Leal et al., 2018). In this sense, Júnior et al. (da Silva Júnior et al., 2021) sought to evaluate traditional Kombuchás flavored with pitanga pulps. They reported lower sugar losses in flavored kombuchas, showing that pre-existing levels of glucose and fructose in fruits contributed to sweeter drinks. Acetic, butyric, citric, succinic and malic acids were identified, as well as terpenes such as curzerene and β-caryophyllene. High antioxidant activity was observed for fruit flavored kombuchas, and among the phenolics identified, epigallocatechin gallate was the most predominant component (over 63%). The most bioaccessible phenolics in flavored kombucha were caffeine (22.38–29.98%), catechin (17.61–23.48%) and hesperidin (22.43–28.47%). After a simulated gastrointestinal digestion, the phenolic contents decreased, influencing the significant drop in antioxidant capacity. The findings showed that pitanga contributes to diversifying and improving the chemical and bioactive characteristics of kombucha.

The quality of meat products varies throughout their shelf life (temperature, presence of oxygen and light, microbial activity). Meat deterioration is caused by lipid oxidation, which can cause undesirable effects, such as loss of essential fatty acids, flavor and discoloration, leading to changes in organoleptic properties (Zamuz et al., 2018). On the other hand, lipid reformulation by replacing a portion of animal fat with fat substitutes containing oils rich in n-3 PUFA can provide healthier characteristics to the food product, thus meeting the demands of health-conscious consumers. In order to improve that, red pitanga leaves extract was added to mutton burgers with fat replacement during storage (at 2 °C). The addition of pitanga extract did not change the proximate composition and acceptance of mutton hamburgers on day 0. The extract also delayed the discoloration of the hamburgers, conferring a more reddish intensity and delayed the oxidation of lipids and proteins over the storage time, decreasing TBARs and carbonyl values and demonstrating a high antioxidant activity on day 18. In addition, the n-6/n-3 ratio was higher in the pitanga haburgers, but within recommended levels (de Carvalho et al., 2019). Thus, results indicate that pitanga extract was effective against color deterioration and lipid and protein oxidation of the meat, without harming sensory characteristics, representing a promising alternative to replace synthetic antioxidants with natural products in lamb hamburgers.

A growing area of research with focus on environmental conservation and industrial development is that which seeks to reverse the toxic effects of environmental stressors (Dartora et al., 2011). In this sense, secondary metabolites from plants with antioxidant activity represent an interesting alternative. Cunha et al., (2019) evaluated the cytoprotective effect of the ethanol extract of *E. uniflora* leaves against mercury chloride. The ethanol extract of *E. uniflora* demonstrated a chelating effect against iron, and these results can be related with total phenols (1079 mg / g) and flavonoids (946.9 mg / g), detected and quantified by HPLC. The same extract showed cytoprotective against mercury and was non-toxic to *D. melanogaster*, with low mortality and low geotaxy inhibition, demonstrating that the extract can reduce the toxicity of this heavy metal against prokaryotic and eukaryotic organisms. From the results, we can conclude that phytocompounds from the ethanol extract of *E. uniflora*, possibly phenols and flavonoids, can be interesting agents to protect different organisms against heavy metal damage through a chelation or antioxidant mechanism.

During this session we could observe that the wide possible applications of *E. uniflora* in new products. Pitanga has great economic potential, due to the sensory characteristics that favor its commercial exploitation, plus the presence of phytochemicals that play an important role in the management of several chronic and degenerative diseases, in addition to representing a hotspot of technological innovation in food, cosmetics and pharmaceuticals.

7. Conclusion

The present review seeks to contribute to the literature, bringing more clarifications about *E. uniflora*. The results of the literature review have revealed that different parts of the pitangueira tree can be used for different purposes because they have a great number of volatile and non-volatile bioactive compounds in its composition.

The phytochemical profile is related to the cultivation of *E. uniflora* which depends on the climate, ripping, storage and preparation of extracts. All these factors can cause variation in the compounds present in the plant's fruits and leaves. The literature has shown that *E. uniflora* fruits and leaves, especially red and purple fruits, have antioxidant compounds in their composition, such as phenolics, flavonoids and carotenoids that have a potential beneficial effect on health which indicates its high value as a functional food.

Data on the toxicological potential of the plant's essential oil and extract are limited but studies have mentioned low toxicity in rodent rates. The application of *E. uniflora* shows a range of biological properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, anti-oxidant, neuroprotective and hepatoprotective effects among others. However, there are no clinical studies on the effects of *E. uniflora* neither biological nor toxicological. Moreover, *in vivo* studies about *E. uniflora* are incipient. Although few studies in humans have reported the profile and biological activities of pitanga, scientific investigation on its phytochemical and biological properties must be conducted, including nutritional and phytochemical profiles in its different botanical parts.

The results obtained in *in vitro* and *in vivo* studies in different models of animals and described in the present review can thus encourage the use of *E. uniflora* in clinical trial, since the studies demonstrate its safety to mammals and the diverse promising effects. Essentially, the results highlight the beneficial potential of *E. uniflora* against several human comorbidities and its use as a nutraceutical, supplement or phytoterapy must be inserted into the pharmacopoiea.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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