



Brazilian Myrtaceae Fruits: A Review of Anticancer Proprieties

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AJT, CBDL, NSF and TOA designed the study and wrote the first draft of the manuscript. Authors NSF and CBDL managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The fruits belonging to *Myrtaceae* family are widely distributed throughout the Brazilian territory and are considered one of the most important families of the Brazilian flora, due to the high prevalence of species edible or used in traditional medicine. Medicinally, the fruits are reported to have antioxidant activity, anti-inflammatory, anticancer, antitumoral activity. Among these properties a lot of research has established that the dietary intake of this fruit has a positive and profound impact on human health and in chronic diseases. Evidences suggest that, rich diets with colored fruits, particularly belonging to *Myrtaceae* family, are highly chemoprotective because of their bioactive compounds. This review showed that the bioactive compounds presents in *Myrtaceae* fruits have anticancer properties and exhibit their chemoprevention effects, elucidating the importance of consuming these fruits.

Keywords: *Myrtaceae* family; cancer; anticancer properties, antioxidant; anthocyanins.

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1. INTRODUCTION

The etiology of various diseases has been associated with oxidative damage induced in cells and tissues, including degenerative diseases such as heart disease, atherosclerosis, pulmonary disorders and certain types of cancer. Nutritional epidemiological studies show a reduction of these diseases in consumers of fruit and vegetables. Thus, an increase in the consumption of tropical fruits due to nutritional, functional and therapeutic properties has been observed worldwide [1].

Foods rich in antioxidants reduce the incidence and mortality from certain cancers. The fruits contain high levels of antioxidants such as polyphenols, phenolic acids, carotenoids, flavonoids and anthocyanins can lower the levels of reactive oxygen species (ROS) in the organisms of mammals and thus avoid damage to DNA and the initiation of mutations that prevent tumor progression [2,3].

The genus *Eucalyptus*, *Malaleuca*, *Eugenia*, *Myrcia*, *Syzygium* and *Psidium* belong to the *Myrtaceae* family [4,5]. They are commonly found in tropical forests from the Amazon to the southern region of Brazil [6]. Among the Brazilian native species, the *Myrtaceae* family stands out for presenting species that produce small fruit and use in traditional medicine. In addition to their use as food, many of these fruits have been used in traditional medical practices due to their important bioactive potential [4].

The protective effect exerted by the fruit has been attributed to the presence of polyphenols, which are the most abundant natural dietary antioxidants. The polyphenol antioxidant capacity may be attributed to the reducing power of the aromatic hydroxyl group responsible for the reduction of reactive free radicals, this activity has been influenced by the number and the position of the OH groups [7].

Among the polyphenols present in foods, there are anthocyanins, which phenolic compounds are belonging to the group of flavonoids that are responsible for the color of bright red to violet fruits. Although currently not considered as a nutrient, anthocyanins have received much attention because of their biological activity. Studies suggest that plant food containing secondary metabolic compounds, when often ingested through the diet, show antioxidant ability in capturing free radicals. This antioxidant action is responsible for conferring beneficial health

effects, including the anti-inflammatory, antimutagenic and anti-cancer properties [8-10].

Jaboticaba (*Myrciaria cauliflora*), malay apple (*Syzygium malaccensis*), jamun berry (*Eugenia jambolana*) stand out amidst the native species *Myrtaceae* family in Brazil because of ease of planting and increased consumption. Because of the evidence that shows important roles in the prevention and in the treatment of chronic diseases such as cancer, this article discusses antioxidants and anti-cancer mechanisms attributed to these *Myrtaceae* family's species.

2. Myrtaceae FAMILY

The *Myrtaceae* family is well defined, with about 140 genera and about 3500-5800 species, found in tropical forests; it is the one of the predominant groups in the Atlantic Forest and is considered one of the most important families of the Brazilian flora, due to the high prevalence of species edible or used in traditional medicine.

All the Brazilian *Myrtaceae* is included in the tribe of *Myrteae*, represented by 23 genera and 1000 species. The main genera of these families are *Eucalyptus* (300 species), *Malaleuca* (100 species), *Eugenicis* (600 species), *Myrcia* (300 espécies), *Syzygium* (200 species) and *Psidium* (100 species) [1-3].

They consist of trees or shrubs aromatic and are characterized by having simple, opposite leaves and aromatic glands. The flowers are regular, hermaphrodite, solitary or aggregated in flowering and fruits usually present in the form of soft or capsule [4].

These fruits are mostly red to purple drupes, with 2–4 cm in diameter, although some species produce larger or less pigmented fruit. In the tropics, these species are often cultivated in home gardens, small-scale agricultural plots, or wild-harvested.

The family has great economic importance, since several species are used in the food they are primarily eaten fresh or used to make jams, desserts, wines, liquors, and vinegars, and can be found in local markets. In addition to their use as food, many of these fruits have been used in divergent traditional medical practices for a variety of illnesses and conditions. The most used parts are leaves, bark and also the fruits that are commonly consumed [5].

3. MYRTACEAE FRUITS

3.1 Jabuticaba

The jabuticaba is the result of jabuticabeira fruit tree that belongs to the *Myrtaceae* family. Its distribution occurs naturally in tropical areas of Brazil and is originally from the Atlantic Forest and can be found from the state of Pará of Rio Grande do Sul, with the highest production of this fruit in the Southeast. Among the currently known species, we highlight the *Myrciaria cauliflora* (DC) Berg and *Myrciaria jabuticaba* (Vell) Berg, the main varieties jabuticaba sabar and So Paulo jabuticaba [11].

The jabuticabeira bears fruit in two periods throughout the year, between August and September and January and February. It is a medium-sized tree, whose leaves are lance-shaped, the flowers are white, the globular fruits that have bark color ranging from red to black and whitish pulp that is both sweet and sour time and quite tasty [12]. The fruits often have only one seed, but may contain up to four [13].

The fruit has a sweet and sub acid taste probably due to its sugar, organic acid and terpene contents [14-15]. Jabuticaba peels are a source of anthocyanins, the flavonoids responsible for the dark color of the fruit. These pigments possess potent antioxidant and anti-inflammatory compounds, with anti-mutagenic and chemopreventive activities [4].

3.2 Jamun Berry

The jambolan is a plant belonging to the *Myrtaceae* family, botanically classified as *Eugenia jambolana* and subsequently reclassified as *Syzygium cumini* [16]. It's also known as jambolo, jambolan, black plum, java plum or jamun, is a native fruit originally from Indonesia and India, can be grown in many countries, because it fits very well in different types of soil and climate. In Brazil, it grows as an ornamental and shade tree in coastal areas and is commonly found in the Northeast.

The *Syzygium cumini* (syn. *Eugenia jambolana*) consists of about 90 genera and 2800 species, it is a large, ever green tree, produces small ovoid fruits that are purple when ripe, its skin is thin, sleek and bonded. Its pulp is also purple is fleshy and involves a large single seed [17]. The taste is smooth, distinctive aroma, although a bit astringent, it is pleasing to the palate, and the

color has great visual impact [13]. Fruiting in Brazil occurs in the period from January to May.

The chemical composition of different parts of these plants contains several active constituents such as flavonoids, gallic acid, ellagic acid and tannins, these bioactive compounds have been considered to possess several medicines properties in the traditional system of medicine, the powdered seeds are a well known Indian folk medicine for treatment of diabetes mellitus [17]. They also have anti-diarrheal, anti-bacterial and anti-inflammatory activities [18]. The pulp and the seeds of jambolan contain in their composition high content of anthocyanins and phenolics that exhibit anticarcinogenic proprieties such as inhibition of the tumor growth [19,20].

3.3 Malay Apple

The jambeiro (*Syzygium malaccense* L. Merr & Perry.) belongs to *Myrtaceae* family, with approximately 3,000 species of trees and shrubs, widely distributed in Brazilian forests and tropical and subtropical regions of the world [21,22]. Despite being originally from Southeast Asia, the jambeiro, can be easily found in the northern, northeastern and southeastern Brazil [23,24]. The fruits of jambeiro are piriform and feature dark red color, slightly sweet, exuding aroma of roses. The natural pigment present in the peel of the red apple indicates the presence of anthocyanins, belonging to the group of flavonoids, which are found only in plant and have colors ranging from deep red to violet to blue. This biological compounds are responsible for therapeutic effects include reduction of coronary heart disease, anticancer effects, antitumor, anti-inflammatory and anti-diabetic, improvement of visual acuity and cognitive behavior, these effects related to its antioxidant activity [25].

4. NUTRITION AND PHYTOCHEMICALS ASPECTS

From a nutritional point of view, this fresh edible fruits have a wide variety of so-called classic nutrients and are excellent sources of carbohydrates, salts, minerals, amino acids, and vitamins, fiber, antioxidants, phenolic compounds and flavonoids, which may vary according to the cultivar, geographical location and growing conditions. Although some of these are present in low concentrations in a given fruit, they may have a significant impact on human health.

Table 1 shows the chemical composition of some fruits of the *Myrtaceae* family [13,26].

The protective effect exerted by the *Myrtaceae* family fruits has been attributed to the presence of polyphenols, which are the most abundant natural dietary antioxidants. These bioactive

compounds include phenols class of phenolic acids and their derivatives, flavonoids, tocopherols, phospholipids, amino acids, phytic acid, ascorbic acid, pigments, and sterols. Bioactive compounds in the fruits *Myrtaceae* family are shown in Table 2.

Table 1. Chemical composition of Brazilian *Myrtaceae* fruits

Nutritional composition (g.100 g-1)	Fruits		
	Jaboticaba	Jamun berry	Malay apple
Carbohydrate	23,02-6,69	17,96 - 8,1	59, 25 - 1,6
Protein	0,2 – 57	4,3 - 0,69	8,62 - 0,3
Lipid	1,7-0,42	1,4 - 0,3	4,51 - 0,2
Fibers	25-9,11	0,91 - 0,24	9,34 - 0,1
Ash	3,82-0,6	1,8 - 0,27	4,17 - 1,2
Moisture	15,33-3,8	87,75-77,72	14,11 - 8,7
Reference	[12,27-29]	[30-33]	[34-37]

Table 2. Chemical composition of Brazilian *Myrtaceae* fruits

Name/ Latin binomial	Part of plant	Bioactive compounds	Biological activity evaluated	Reference
Jaboticaba (<i>Myrciaria cauliflora</i>)	Peel	Flavonoids, anthocyanins, phenolics compounds, and antioxidant activity	Anti-inflammatory compounds, anti-mutagenic, anti- HIV anti-microbial activity,antibiotic, antiproliferative and anticancer	[14,15,38]
Jaboticaba (<i>Myrciaria jaboticaba</i>)	Peel	Tannis, ellagic acid, rutin, and quercetin	Cancer chemopreventive and nonteroidal antinflatomores	[39]
Malay Apple (<i>Syzygium malaccensis</i>)	Peel, pulp, seeds and leaves	Anthocyanins, carotenoids, flavonoids and gallic acid	Astringent, antibacterial, antiviral, anti-diarrheal, antidiabetic activity, Reduction of coronary disease, anticancer effects, antitumor, anti-inflammatory, anti-virus, and inhibition of the complement system	[22,23] [25,40] [18,21,25]
Jamun Berry (<i>Eugenia jambolana</i> / <i>Syzygium cumin</i>)	Peel, pulp, seeds	Flavonoids, gallic acid, ellagic acid and anthocyanins	Anti-bacterial, anti-HIV, anti-diarrheal, antidiabetic activity,anti fungal, anti-inflammatory, anti-bacterial, anti- HIV, anti-helminthic and anticancer	[16,18,19, 41,42]

The bioactive compounds such as vitamins, phenolics and pigments are mostly secondary metabolites, which generally are related to the plant defense systems against ultraviolet radiation or the attacks of insects or pathogens, but in humans in low concentrations, play an important protective role as agents antioxidants capable of inhibiting or retarding the oxidation of various substrates [43,44,45].

Studies suggest that plant food containing secondary metabolic compounds, which, while often ingested through the diet, has antioxidant capacity in capture of free radicals responsible for conferring beneficial health effects, including the anti-inflammatory with antimutagenic and anti-cancer properties [8,9].

5. ANTIOXIDANT ACTIVITY OF MYRTACEAE FRUITS

Reactive oxygen species (ROS) are produced naturally in biological systems as a result of oxidative metabolism. The origin also can be exogenous, such as ultraviolet light, ionizing radiation and chemical agents. The ROS is a consequence of normal cell metabolism, but also may be due to pathological processes, like that occurs in the inflammatory response. However, ROS damage cell membranes and DNA, causing cancerous mutations and the oxidation of low-density lipoprotein is a major factor in the promotion of heart disease. ROS are also implicated in activating redox-responsive pro-inflammatory transcription factors, nuclear factor (NF)- κ B and activator protein (AP)-1 [46].

Repeated damage caused by ROS throughout the span of a human life increases with time, and is a major cause of age-related cancers and other oxidatively induced diseases. Oxidative damage is balanced by endogenous antioxidants, but additional protection, provided by nutritive and non-nutritive elements from food, is critical for disease chemoprevention [47].

There is increasing interest in the antioxidant activity of the photochemical present in the diet, since they play a very important role in the organism's defense system against ROS, which are mainly generated during the regular energy metabolism of aerobic cells [48]. It has also been proposed that the antioxidant activity of plant origin components can be mainly ascribed to the presence of phenolic compounds [49]. The family *Myrtaceae* has been studied for years and their aromatic terpenoid and polyphenolic substances

have been described [50]. Many known antioxidant flavonoids have been isolated from all parts of many species in this group.

Jaboticaba has been reported to be rich in phenolic constituents, including resorcinol, p-hydroxybenzoic acid, hydroxycinnamic acids, flavonoids, coumarins, anthocyanins and ellagitannins [51]. Many flavonoids and related polyphenols are actually have been shown to be better antioxidants than vitamins. The flavonoid biological activity is large, one of them is scavenging free radicals and ROS and anti-inflammatory activity [47]. The flavonoids identified from *M. cauliflora* were isoquercitrin, quercimeritrin, quercitrin, myricitrin, quercetin, and rutin [4].

Jaboticaba is known as one of the richest Brazilian sources of anthocyanins. Some recent papers have demonstrated that the biological (antioxidant, antiradical, etc.) activities of jaboticaba skin extracts are due to their high phenolic compounds content [28]. The main contribution to the total phenolic contents of the whole fruit came from the peel [28,52].

Extracts from different parts of jaboticaba were investigated for their antioxidant activity. Most studies have focused on the alcohol extracts of flesh or peel from jaboticaba, but the report of Wang et al. (2014), was the first to reveal that the best antioxidant and cancer chemopreventive activity exists in the water-soluble seed extract. The results of the determination of antioxidant activity of different extracts using two methods (DPPH and ABTS) demonstrated the very potent antioxidant activity of the water extract of seed [53].

Leite-Legatti et al. [28] showed high antioxidant activity at three different assays: 25,514.24 \pm 3037 μ M TE g⁻¹ (ORAC), 45,35 \pm 0,50 μ g mL⁻¹ (DPPH), and 9458 \pm 97 μ M TEAC g⁻¹ (ABTS) [26]. Others studies reported the antioxidant capacity of jaboticaba using different methods (HOCl scavenger, ABTS and DPPH, FRAP, and β -carotene bleaching), all of them confirm the fruit's antioxidant activity [54-55].

Reynertson et al. [39] analyzed the antiradical phenolic constituents from fourteen edible Myrtaceae fruits. This study related that *M. cauliflora* is the most active extract in the DPPH assay (19.4 μ g/mL), with only a slightly higher than average TPC (31.6 mg GAE/g) and TEAC (2.78 mg/g) [37]. The antioxidant

properties are related to several mechanisms of action including the capture of free radicals and the inhibition of generation of reactive species during the cell metabolism. [2,3]. Anthocyanins are considered antioxidants because they are able to stabilize free radicals by hydrogen radical donation [56,57]. There is as the fundamental structure flavilic cation and at least one glycoside unit, which is generally attached at the 3 position of the ring C. 'of the B ring, in particular in positions 3' and 5' This ability is related primarily to the catechol group present in the ring B which is easily oxidized, forming a very stable species [57,58].

It is not unusual for fruits collected from different geographical locations to have different phytochemical profiles. Indeed, the anthocyanidins present in the *Eugenia jambolana* were described in Li et al. [59] study in the order of relative proportion of petunidin>malvidin>delphinidin>cyanidin>peonidin while the Brazilian berries had delphinidin>petunidin>malvidin>cyanidin>peonidin. The anthocyanins are a group of well-studied phenolic compounds with antioxidant, anti-inflammatory, antimutagenic, and cancer chemopreventative activities [14].

Vasi and Austin [60] evaluated the antioxidant potential of *Eugenia jambolana Lam.* seeds through DPPH radical-scavenging activity, reducing power determination - Fe (III) reduction, ABTS radical cation decolorization assay and determination of antioxidant activity by FTC method. The maximum percentage inhibition of DPPH was 53.47% (800 µg). By ABTS and nitric oxide assays were 98.92 and 52.46% (1000 µg), respectively, and by ferric ion was 94.43% (800 µg). The total antioxidant activity of *E. jambolana* seeds were 2.09 g equivalent to vitamin E and the reducing power was found to be 28.94 g equivalent to vitamin C.

Reactive oxygen species (ROS) cover a wide range of chemical components, including superoxide anion, hydrogen peroxide, hydroxyl radicals, nitric oxide, peroxyxynitrite, these radicals have potential to initiate degenerative processes in human body [61]. Anand et al. [62] described the antioxidant potential of the fruit pulp preparation under the oxidant-exposed conditions in Leydig cells in vitro by the first time. In this study, the active ingredient was found in *Eugenia jambolana* fruit pulp. It helped in reducing the formation of thiobarbituric acid

reactive substances while improving the activities of antioxidant enzymes, SOD, catalase and GST. *Eugenia jambolana* extract was able to regulate nitric oxide synthase (iNOS) expression leading to nitric oxide (NO) depletion in the target cells. These results show that the fruit pulp of *E. jambolana* possess antioxidant properties having the capacity to mitigate the oxidative stress in Leydig cells induced by H₂O₂.

Sultana et al. [63] investigated the antioxidant activity of extracts from barks trees by different antioxidants assays (linoleic acid peroxidation system; DPPH; reducing power). Among different barks, *E. jambolana Lam.* was found to offer the most efficient antioxidant activity. The maximum percentage of inhibition of linoleic acid was noted by absolute ethanolic extract of *Eugenia jambolana bark* (90.6%). Furthermore, by the linoleic acid assay and auto-oxidation of β-carotene, Bajpai et al. [64] have observed that the hydromethanolic extract of the jamun seed was effective in scavenging (90.6%) free radicals due to the presence of high total phenolic content in the extract.

Syzygium malaccense is specie from *Myrtaceae* fruits that have been showing potential antioxidant activity. Arumugam et al. [65] demonstrated that the ethanolic leaf extract of *S. malaccense* displayed a moderate total phenolic content with reasonable free-radical-scavenging properties. It reported the antioxidant potentials of a standardized extract of *Syzygium malaccense* using DPPH, ABTS and NO free-radical-scavenging assays. Among the three different antioxidant assays, the extract was able to scavenge DPPH (16.65 µg/ml) and ABTS (47.27 µg/ml) radicals far better than the nitric oxide radicals (333.00 µg/ml).

Savitha et al. [66] used different assays (DPPH, hydroxyl radical scavenging activity and reducing power) to determine and compare the antioxidant properties of selected *Syzygium malaccense*. Based on the estimation of total polyphenols and antioxidant scavenging assays, the study concluded that methanolic extract of *Syzygium malaccense* showed most potent antioxidant activity when compared to aqueous leaf extract. Furthermore, Ikram et al. [24] analyzed antioxidant capacity and total phenolic content of Malaysian underutilized fruits. The results obtained to assays *Syzygium malaccense* were 17.01% and 0.22 mM by DPPH and FRAP assays.

Based in these reports, *Myrtaceae* fruits may show potential antioxidant capacity and can be considered a good source of natural antioxidants, preventing the harmful effect of free radicals. Aimed at improving health, the consumption of these natural sources of substances can be vitally important to the human body. Phenolic compounds and anthocyanins contributes to the maintenance of pro and antioxidant balance of biological systems, playing key role in the prevention of various diseases, including cancer.

6. ANTICANCER PROPRIETIES OF *Myrtaceae* FRUITS

Cancer is characterized as a major public health problem in both developed and developing countries, being characterized as a multifactorial disease with complex interactions [67]. According to the National Cancer Institute (INCA-Brazil), cancer is the name given to diseases that have common genetic changes that result in uncontrolled growth of cells that invade tissues and organs and can spread to other parts of the body. Cancer of the training process or carcinogenesis goes through several stages to reach the tumor formation [68]. The incidence of the disease is related to environmental factors, genetic predisposition, obesity and especially dietary [69]. Some studies have shown that eating habits play a fundamental role in the etiology of cancer. According to Fortes et al. [70], about 35% of cancer cases are related to an improper diet.

In the pathogenicity of cancer, oxidative stress effects are demonstrated. These effects are counteracted and/or prevented by antioxidants. The investigation of the action mechanism that antioxidant substances have can be an important point to improve the knowledge in the science area. Some of these substances are the polyphenols, present in the *Myrtaceae* fruits. The antioxidant properties of polyphenols are based on their ability to be oxidized by, for example, hydrogen peroxide, to phenyl ketones (Quinones). Another mechanism described is the capacity of scavenge hydroxyl radical (\bullet OH) by virtue of their addition to double bonds with the formation of a corresponding hydroxyl derivative. The structure of the polyphenols, how the absence or presence of an electron in a carbon-carbon bond in an aromatic or aliphatic compound contributed to these properties [71].

Each year, new evidences suggests the role of diet in cancer prevention and treatment, including

results of studies involving various foods, phytochemicals, and nutrients; use of complementary and alternative approaches for prevention and treatment; and optimal diets for those wishing to prevent cancer or its recurrence. Currently, a huge attention has been given to strategies that may prevent cancer, and the consumption of functional food with chemopreventive properties can play as anti-carcinogenic, antioxidant, and anti-inflammatory factors. They can also act against cancers that are induced or sustained by hormones, or they may have antiangiogenic activity [72,73]

Some studies have linked consumption of colorful fruits and vegetables with the reduces risk of breast cancer and colorectal polyp recurrence due to the presence of bioactive compounds, because they act as chemoprotectors, acting in inducing enzymes that metabolize carcinogens, turning them into their less reactive forms [74,75].

Among the bioactive compounds, the consumption anthocyanins and flavonoids presents in *Myrtaceae* fruits are associated to reduce risk of chronic diseases, including cancer. These compounds here attracted a great interest because antioxidant activity can reduce levels of ROS in mammals and thus prevent DNA damage and mutations that prevent initiate tumor progression [2,3]. These evidences are described below and summarized in Table 3.

Extract rich in anthocyanins exhibit strong anti-proliferative activity against different cancer cell lines. The freeze-dried jabuticaba peel (JP) extract contains two major compounds: delphinidin 3-glucoside and cyanidin 3-glucoside. The inhibitory effects in these extracts were submitted to a partition on dichlorometane and ethanol affording apolar jabuticaba peels and polar jabutibaca peels extracts. The non-polar JP extract was active against the prostate cancer (PC-3 cells - $IC_{50}=13.8 \mu\text{g mL}^{-1}$), and leukemia cells K-562 ($IC_{50}=15.8 \mu\text{g mL}^{-1}$) [28].

There is evidence that jabiticabin, a flavonoid compound extracted from *M. cauliflora*, exhibited anti-proliferative effects against HT-29 ($IC_{50}=65 \mu\text{M}$) and HCT116 ($IC_{50}=30 \mu\text{M}$) colon cell lines. This extract is rich in anthocyanins, phenolic acids, and flavonoids with anti-radical, anti-inflammatory, and cytotoxic activity, and therefore we believe it has potential to be developed as a functional food [4].

Table 3. Anticarcinogenic activities of Brazilian *Myrtaceae* fruits in different cancer cell lines or animal models

Cell/ Animal model	Major compounds of Brazilian <i>Myrtaceae</i> fruits	Anticarcinogenic Activities	Reference
HS578T	Cyanidin 3-glucoside peonidin 3-glucoside	(-) tumor growth; Induce apoptosis.	[76]
Apc ^{Min} mice	Cyanidin 3-glucoside anthocyanin mixture	↓numbers of small-sized; adenomas; ↓adenomas; ↓efficacy oxidative DNA adduct levels in intestinal adenomas.	[77]
HO-8910PM Nude mice	Cyanidin 3-glucoside	↓Down-regulation of mucin- 4 protein; Induce apoptosis; (-) proliferation of ovarian cancer cells; ↓positive expression of Ki- 67 and mucin-4 in tumors.	[78]
MCF7 ^{ErbB2} MDA-MB231 BT474	Cyanidin 3-glucoside	blocks ethanol-induced activation; ↓ethanol-induced breast cancer metastasis.	[79]
JB6 A549 Nude mice	Cyanidin-3-glucoside	(-) tumor promoter-induced carcinogenesis ; (-)tumor metastasis; blocked TPA-induced neoplastic transformation; (-) UVB- and TPA-induced transactivation of NF-κB and AP-1 and expression of cyclooxygenase-2 and tumor; necrosis factor-α; ↓tumor xenograft growth size; ↓non-malignant and malignant skin tumors; (-) proliferation of a human lung carcinoma cell line.	[80]
A549	Cyanidin 3-glucoside	↓the activation of c-Jun and NF-κB; ↓cell–matrix interaction. (-) expressions of u-PA and MMP-2; (-) effects on the invasion and motility of tumor cells;	[81]
HSC-3	Cyanidin 3-glucoside	↑ Level of active caspase- 3; Induce apoptosis; (-) Survivin and Induction of Bid Cleavage; induce apoptosis.	[53]
K-562 PC-3	delphinidin3-glucoside cyanidin 3-glucoside ellagic acid	(-) proliferation of leukemia cells and neoplastic cells.	[25]

Cell/ Animal model	Major compounds of Brazilian <i>Myrtaceae</i> fruits	Anticarcinogenic Activities	Reference
HT-29 HCT116	jaboticabin, cyanidin 3-glucoside delphinidin 3-glucoside.	(-) chemokine interleukin (IL)-8	[4]
MDA-MB-231 MDA-468 MCF-7 A549	Cyanidin-3-glucoside, peonidin-3-glucoside Ellagic acid/ellagitannins	Induce apoptosis; ↓ tumor size. ↓ viable cell number of human lung cancer cell line	[82] [83]
DMBA	Ascorbic acid, gallic acid, tannins, anthocyanins.	↓enzymes CAT and SOD; ↑free-radical scavenger; ↓activity of tumor promoters; (-) effects on mutagenesis and carcinogenesis; ↓levels of glutathione, superoxide dismutase, catalase and protein and enhancement.	[84]
TRAMP mice	Gallic acid	↓tumors ↓apoptotic cells ; ↓expression of Cdc2, Cdk2, Cdk4, Cdk6, cyclin B1 and E.	[85]
JB6	Myrcitin	(-) epidermal growth factor (EGF)-activated cell transformation; modulating DNA-binding and transcriptional activity of STAT3; (-)UVB-induced skin cancer	[86,87]
COLO 320 DM	β- sitosterol	Induce dose-dependent growth inhibition; induce apoptosis; (-) expression of β-catenin and PCNA antigens.	[88]
MCF-10A MCF-7aro MDA-MB-231	Delphinidin 3,5-diglucoside and cyanidin 3,5-diglucoside	pro-apoptotic effects; (-) growth; induce apoptosis.	[59]
HCT-116 colon CSCs	Delphinidin-3, 5-diglucoside, cyanidin-3, 5-diglucoside, petunidin-3, 5-diglucoside.	(-) proliferation; induce apoptosis; ↑activation of capase 3; ↑activation of caspase 7	[89]
HL60 HCT116	Anthocyanidins (delphinidin, malvidin, peonidin, cyanidin, and pelargonidin) and flavonols (myricetin, quercetin, and kaempferol)	(-) cancer cell growth; (-) apoptosis in cancer cells	[90]
CaSki cells	Ellagic acid	↓mitotic rate; ↓rate of cell proliferation; (-) overall cell growth; induce apoptosis; activation of the cdk inhibitory protein p21;	[91]

Cell/ Animal model	Major compounds of Brazilian <i>Myrtaceae</i> fruits	Anticarcinogenic Activities	Reference
T24	Ellagic acid	induce G1 arrest. ↓ viable cells; induce G0/G1-phase arrest of the cell cycle; induce apoptosis; ↑ p53 and p21; ↓ CDK2 gene expression; promote caspase-3 activity.	[92]
22Rv1 DU145 Nude mice	Gallic acid	↓ cell viability via apoptosis induction; (-) tumor cell proliferation; ↓ microvessel density	[93]

Legend: (-) inhibit or suppressed; ↓ reduce, decrease; ↑ increase.

Wang et al. [53], in their study, evaluated the effect of the water extract from different parts of jaboticaba on oral cancer cell line (HSC-3). Water extracts of jaboticaba seeds showed important anti-proliferative effects. The IC₅₀ of jaboticaba seed/water extract was approximately 15 µg/mL and jaboticaba seeds also induced oral cancer cell apoptosis by decreasing the expression of survivin. These results show the potential of jaboticaba seed extract as a chemopreventive agent.

Regarding of jamun berry, Aqil et al. [83], evaluated the inhibition of cell proliferation by jamun extracts in human non-small cell lung carcinoma cell line (A549). The hydrolyzed jamun pulp showed strong anti-proliferative activity with an IC₅₀ value of 59±4 µg/ml. The hydrolyzed seed extract showed highest anti-proliferative activity (IC₅₀ = 38±3 µg/ml). This extract of jamun pulp contained all five major anthocyanidins in different proportions. The anti-proliferative activity of individual anthocyanidins has been shown in different cancer types. The activity in the jamun hydrolyzed and unhydrolyzed seed extracts may be attributed to the high content of polyphenolics compounds including various ellagitannins.

Li et al. [59] investigated the anti-proliferative and pro-apoptotic effects of jamun fruit extract in estrogen dependent/aromatase positive (MCF-7aro), and estrogen independent (MDA-MB-231) breast cancer cells, and in a normal/non-tumorigenic (MCF-10A) breast cell line. The extract of jamun fruit was most effective against MCF-7aro (IC₅₀=27 µg/mL), followed by MDA-MB-231 (IC₅₀=40 µg/mL) breast cancer cells. Importantly, the extract of jamun fruit exhibited only mild anti-proliferative effects against the

normal MCF-10A (IC₅₀>100 µg/mL) breast cells. Similarly, the extract of jamun fruit (200 µg/mL) exhibited pro-apoptotic effects against the MCF-7aro and MDA-MB-231 breast cancer cells, but not towards the normal MCF-10A breast cells. Jamun fruit extract also exhibited the most potent cytotoxic activity against MCF7 breast carcinoma cells (IC₅₀=5.9 µg/mL).

Pamar et al. [84] describes the anticancer efficacy of *Syzygium cumini* against DMBA-induced skin cancer in mice. The inhibition of tumor incidence by hydro-alcoholic extract of *S. cumini* seed was evaluated in mice on two stage process of skin carcinogenesis. The extract was able to induce reduction in tumor incidence to 37.5, 50 and 25% respectively in comparison to the carcinogen treated control. The *Syzygium cumini* seed can be used as a potential cancer chemopreventive agent by virtue of its efficacy in stimulating the antioxidant defense system.

Rabeta et al. [94] evaluated the action of methanolic extracts of malay apple and found a significant anti-proliferative effect with 79% cell viability in MCF-7 breast cancer cell line (IC₅₀ =632.3 µg/ml). This finding revealed that this fruit extract exhibit anti-proliferative activity against MCF-7, which is strongly estrogen-dependent, probably due to extract compound responsible for its anticancer properties. Furthermore, Wongwattanasathien et al. [95] also showed anti-proliferative effect of malay apple in MCF-7 cell line.

Fig. 1 represents the possible mechanisms of Brazilian *Myrtaceae* fruits again the development of cancer. These data report the inhibitory activity of extracts rich in anthocyanins and in flavonoids.

They also have high antioxidant activity against different human cancer cell lines. The literature reports only a few studies about the anticancer and anti-proliferative activity associated to *Myrtaceae* fruits and cancer protection. Based on these results, jaboticaba, malay apple and jamun berry are promising not only as a source of antioxidants but also as a chemopreventative agent.

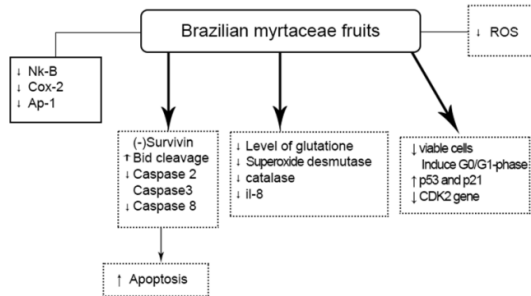


Fig. 1. Possible mechanisms of Brazilian myrtaceae fruits against the development of cancer

7. CONCLUSION

Jaboticaba, jamun berry and malay-apple are a potentially rich source of many dietary phenolic antioxidants and are believed to play an important role in the prevention of many oxidative and degenerative diseases, including cancer. Novel agents who would provoke the cure or prevent cancers are still very much needed. This review showed that the bioactive compounds presents in Myrtaceae fruits, have anticancer properties and exhibit their chemoprevention effects, emphasizing the importance of consuming these fruits. Moreover, the concentrations of different polyphenols and other substances presents in Myrtaceae fruits and the interactions between them have yet to be fully elucidated; therefore, more information is needed with regards to the possible role of Myrtaceae fruits in cancer prevention and therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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