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Effects of Camu-camu (*Myrciaria dubia*) on human health: A systematic review

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Abstract
Camu-camu (*Myrciaria dubia*) belongs to the Myrtaceae family and is a shrub native to the Amazon rainforest, with fruit that has a potent antioxidant capacity due to its high content of vitamin C and total phenolics. It has antioxidant and anti-inflammatory properties, antigenotoxic effects, and improves the biochemical profile. It can be used as a functional dietary supplement to delay aging and control chronic diseases associated with diabetes, obesity, and cancer. For these reasons, this study aims to perform a systematic review regarding the effects of Camu-camu on human health. Databases such as PUBMED, EMBASE, and Scielo were searched following the PRISMA guidelines. After the literature search and after applying the inclusion and exclusion criteria described above, we included 12 studies. The growing interest in Camu-camu occurs due to its high ascorbic acid content (200 to 700 mg/5 g) associated with other antioxidant compounds and the alleged effects, culminated in several dried products that are found in the international market for a premium price. In health, this plant's use both in humans and in animal models has shown antioxidant, anti-inflammatory, antimutagenic, hypoglycemic, hypolipidemic actions. It also prevents visceral and liver fat deposition due to brown adipose tissue activation and increased expenditure of energy. Moreover, the use of Camu-camu can lead to flow-mediated vasodilation responses and blood pressure modifications. The studies found in the literature show that this plant can be used as a nutraceutical once it exhibits impressive amounts of bioactive compounds that can produce antioxidant and anti-inflammatory actions and, for these reasons, could be considered to prevent several pathological conditions such as diabetes, dyslipidemia, metabolic syndrome, cardiovascular diseases, and cancer.

Keywords: Camu-camu, *Myrciaria dubia*, antioxidant, anti-inflammatory

1. Introduction
Natural antioxidants are valued because they can be used to design beneficial health foods (functional or nutraceutical). The importance of antioxidants is crucial for health due to their ability to neutralize free radicals, being responsible for many degenerative diseases such as cataracts, atherosclerosis, and cancer [1, 2]. The Camu-camu (*Myrciaria dubia*), also known as caçari, araçá of water, or sarão, is a species belonging to the family Myrtaceae. It is a shrub native to the Amazon rainforest, with round berries with an average diameter of 2.5 cm. This fruit has a high antioxidant capacity due to its high content of vitamin C and total phenolics (1,420 mg GAE 100 g-1). On dry land soils, where nutrients and water can be controlled, the camouflage can produce more than two annual harvests, as with other species of Myrtaceae, such as jabuticaba (*Myrciaria cauliflora*), acerola (*Malpighia glabra*) and araçá-boi (*Eugenia stipitata*) [3, 4]. In the Amazon, the fruits of camu plant are collected mainly by local farms and used to prepare juices, sweets, and liquors. The juice, made with ripe fruit, has a pinkish-red color, promoted by anthocyanins, a powerful antioxidant [5]. In addition, camu camu contains aldose reductase inhibitors, anthocyanins, and the hepatoprotective compound 1-methyl malate. It has antioxidant and anti-inflammatory properties, antigenotoxic effects, and improves the biochemical profile. As such, it can be used as a functional dietary supplement to delay aging and control chronic diseases associated with diabetes, obesity, and cancer [6-8]. Studies have revealed 30 different phenolic compounds in the fruit of camu-camu, especially flavan-3-ols, ellagic acid and its derivatives, flavonols, and flavonones. In addition to polyphenols, camu-camu also has carotenoids, mainly trans lutein and β-carotene [9, 10]. Camu-camu is known as the richest vitamin C fruit known, ranging from 800 to 6,100 mg / 100 g of pulp. The ripe fruit has a higher content than the green fruit, unlike the acerola. Therefore, it has the potential to prepare foods rich in vitamin C (furrow, nectar, carbonated soft drink,

jelly, ice cream, chocolates, candies), cosmetics (face cream, shampoo, and conditioner) and drugs [11, 12]. The commercialization of Camu-camu is done on a small scale, in fairs, in the producing region. However, the significant part is made in the form of frozen pulp. The fruit is very little known within the country, but it is highly sought after by the Japanese, Americans, and Europeans, being exported in refrigerated containers. In Japan, the pulp is transformed into carbonated drinks, vinegar, snacks, ice cream, candies, and tablets. Some studies show that it can be used in the preparation of yogurt [10, 13, 14].

In view of the above, this paper aims to review the literature on the effects of Camu-camu on human health.

2. Methods

2.1 Data source

This review was carried out at MEDLINE-PubMed (National Library of Medicine, National Institutes of Health), EMBASE, and Scielo databases were searched and following the PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines. This review aimed to answer the following focal question: Do Camu-camu or its derivatives promote beneficial effects on human health?

2.2 Search

This research included articles published in the last ten years (July 2011 to August 2020) and considered clinical trials, double-blind, randomized, placebo-controlled studies, retrospective case-control studies, and studies with animal models. The combination of terms used for the search were: camu-camu or *Myrciaria dubia* and antioxidant effects or anti-inflammatory or health effects.

2.3 Eligible criteria and study selection

This review included quantitative and qualitative studies that demonstrated the effects of Camu-camu and its bioactive compounds on human health. Exclusion criteria were articles not in English or Portuguese, literature reviews, and letters to the editor.

2.4 Data extraction

Two authors searched the databases independently according to the descriptors and inclusion and exclusion criteria. The results were extracted from eligible articles that clearly indicated the author, date, sample size, study design, and gender.

3. Results and discussions

After the literature search and after applying the inclusion and exclusion criteria described above, we included 12 studies. Three of them were studies in humans, and nine were studies performed in animal models (rats, mice, and fish). Figure 1 shows the study selection.

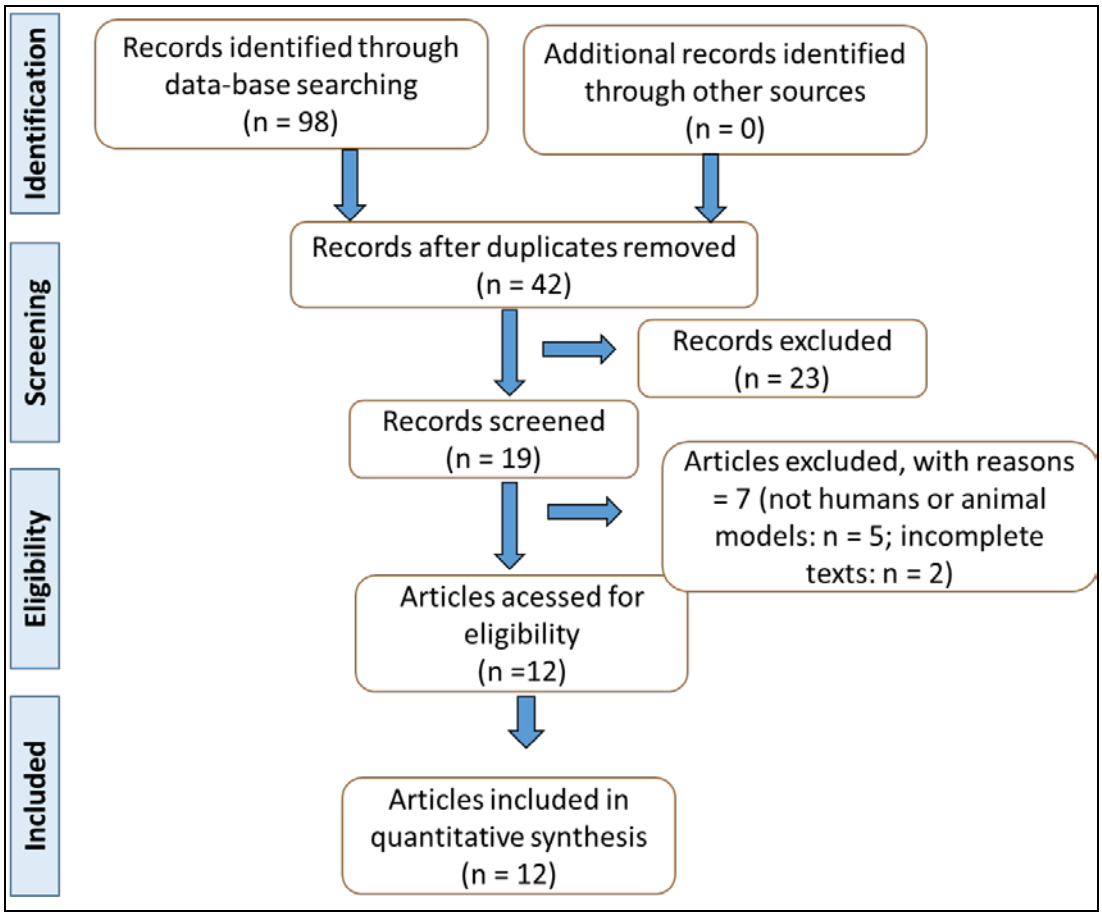

Fig 1: Flow diagram showing the study selection, according to PRISMA guidelines [15].

3.1 Camu-camu in a nut shell

Camu-camu (*Myrciaria dubia*, Myrtaceae family) is an Amazonian fruit *from a* native shrub commonly found in areas that are flooded for 3-4 months of the year. This species is impressive for its capacity to synthesize and accumulate significant amounts of several health-promoting phytochemicals [3]. The round fruit is about 2.5 cm in diameter, and with one to four seeds. The berries possess a red-to-purple pericarp and a very juicy, tart acid, and pink mesocarp [14].

Due to the very high acidity, the fruit is not consumed *in natura*, but they are used in juices, and mostly pulp, is used in beverage production and as a food ingredient [16]. The growing interest in Camu-camu occurs due to its elevated ascorbic acid content (200 to 700 mg/5 g) associated with other antioxidant compounds and the alleged effects, culminated in several dried products that are found in the international market for a premium price. These products include a variety of foods and cosmetics (US$ 140 to 440 per kg) [17] and are mainly prepared with fruit pulp and skin. The seeds are commonly discarded, but some studies have shown that seed extracts possess a rich and varied chemical profile, such as gallic acid, methylvescalagin, ellagic acid, and proanthocyanidin A2. Other compounds such as castalagin, vescalagin, quercetin-3-rutinosid, (+)-catechin, and (-)-epicatechin are also found [10, 13, 18]. Figure 2 summarizes some beneficial effects of Camu-camu,

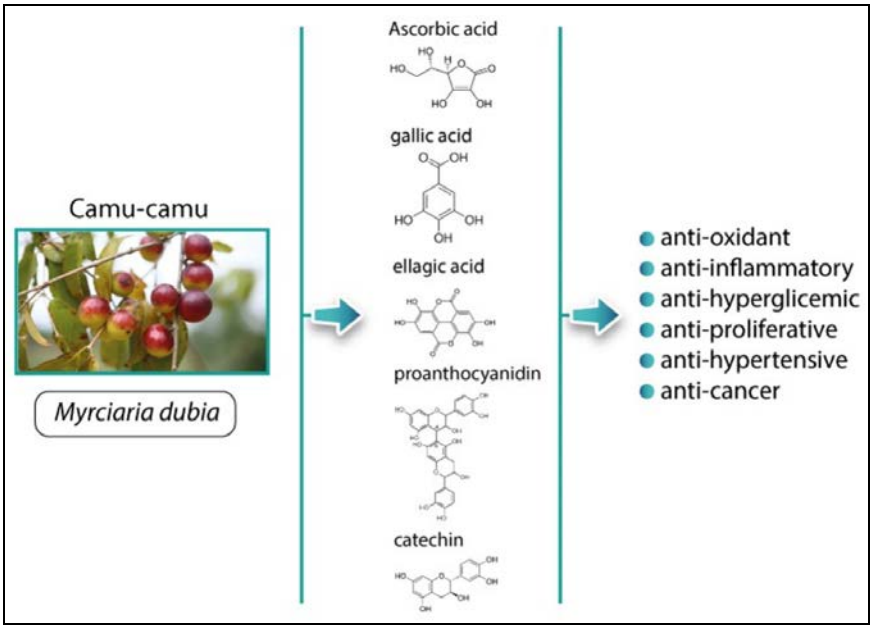

Fig 2: The phytochemicals present in Camu-camu exhibit important antioxidant, anti-inflammatory, and other benefits to human health.

3.2 Effects of Camu-camu

Our review shows that shows that only three studies evaluated the effects of Camu-camu in humans [20, 21, 27] and nine studies were performed in animal models [8, 22-26; 28-30]. The studies performed in humans showed the potential of a single dose of Camu-camu in reducing blood pressure and improvement in vasodilation responses [20]. Moreover, the use of this fruit in smokers reduced the levels of pro-inflammatory cytokines and reduced oxidative stress [21]. The interesting thing about this latest study is that Camu-camu was better for producing anti-inflammatory and antioxidant effects than the same content of ascorbic acid administered in the comparative group. The study of Vargas *et al*. [27] showed significant augment of serum ascorbic acid and a significant reduction in the glycemia, total cholesterol and HDL-cholesterol levels in the participants that consumed capsules of Camu-camu. They also showed significant reduction in LDL-cholesterol levels. Nevertheless, these three studies were performed in a small sample of subjects (two of them included only twenty participants and one study included eighteen subjects) and the authors did not use a placebo group [20, 21]. These facts can represent relevant biases in these trials.

Studies with rats have shown that the use of Camu-camu can have antimutagenic effects [22], reduces fat liver deposition [8], decreases body mass index [23, 29], has nephro-protective effects [24] and significantly improves the lipid profile [28-30]. In fish, there is a significant improvement in physiological parameters for the rearing of these animals [25] and produces an improvement in immune response [26].

Other investigations were performed with Camu-camu. In a study based on *in vitro analysis*, Do Carmo *et al*. [18] showed that the extracts of Camu-camu exhibited antischistosomicidal and antimalarial activities possibly due to the toxic effects attributed to methylvescalan and 2,4-dihydroxybenzoic acid. The anti-hemolytic effect was related to methylvescalagin. They did not observe toxic effects for leishmaniasis [18].

In a systematic review, Pardo-Aldave *et al*. [7] evaluated eleven in vitro studies that showed positive antimicrobial effects on gram-positives. One study showed that this plant could have better effects than an antibiotic.

Fidelis *et al*. [10] evaluated the antioxidant capacity of Camu-camu seeds in an optimized solvent system that augmented the extraction of phenolic compounds, where castalagin and vescalagin were the main components. The extract exhibit antioxidant, antiproliferative and cytotoxic capacity against A549 and HCT8 cancer cells. Moreover, the authors also observed antimicrobial effects (protection of human erythrocytes against hemolysis), down-regulated the enzymes α-amylase and α-glucosidase, and produced *in vitro* antihypertensive actions. Moreover, the extract inhibited *in vitro* human LDL oxidation and decreased the release of TNF-αand the activation of NF-κB in macrophages cell culture. These results showed that camu-camu seed might be a way to recover active compounds.

The study performed by Fidelis *et al*. [9] showed that the major bioactive compounds of a lyophilized Camu-camu seed extract were Gallic acid, vescalagin, procyanidin A2, and epicatechin. They also observed antioxidant activity, inhibition of cell proliferation of human hepato-carcinoma cells, and human colorectal adenocarcinoma epithelial cells. Inhibition of the enzymes α-glucosidase andα-amylase, and angiotensin-converting enzyme, was also observed. The addition of this extract to yogurts increased the antioxidant capacity showing that it could be used as food ingredients.

The seed extract of camu-camu may also exhibit cyto-protective effects of HCT8 cancer cell line and protective effect against induced-cisplatin chromosomal breaks index. These results suggest antimutagenic properties that could be linked to the antioxidant and cytotoxic activities of the bioactive compounds [19].

4. Conclusion

The studies found in the literature show that this plant can be used as a nutraceutical once it exhibits impressive amounts of bioactive compounds that can produce antioxidant and anti-inflammatory actions, and can improve body weight, glycemia and serum lipids. For these reasons, could be considered to prevent several pathological conditions such as diabetes, dyslipidemia, metabolic syndrome, cardiovascular diseases, and cancer. However, more clinical trials with human beings (and with larger samples) need to be performed in order to know the doses and better way of administration so that pathological conditions related to oxidative stress and inflammatory processes can be prevented or even treated with this plant with so many medicinal qualities.

References	Model of the study	Intervention	Main results	Conclusion
Studies in humans				
Miyashita *et al.* [20]	Cross-over design with 20 healthy youngs (10 men and 10 women; 18–28 years) / Japan	Participants received a single oral dose of CC pericarp extract or placebo.	The single dose of CC led to flow-mediated vasodilation responses and blood pressure modifications.	CC can be used as a functional food resource.
Vargas *et al.* [27]	18 participants of both sexes (11 women and 7 men; 21-35 years) / Brazil	Participants were divided into a group that received daily CC capsules (320 mg of vitamin C) and a control group that received daily capsules with 320 mg of synthetic vitamin C.	There was an increase in ascorbic acid serum levels and a significant reduction in blood glucose, LDL-c, and CT in the group that received CC. In the group that received synthetic vitamin C there was a significant reduction in blood glucose.	The capsule of CC showed hypolipidemic and hypoglycemic action, thus showing the potential health benefits of vitamin C and CC.
Inoue *et al.* [21]	Clinical trial with 20 male smoking volunteers; 32-45years / Japan	Subjects were assigned to take 70 mL/d of 100% camu-camu juice (corresponding to 1050 mg of vitamin C (CC group; n=10) or 1050 mg of vitamin C tablets (vitamin C group; n=10)/7d, and to continued smoking.	There was a reduction in the levels of oxidative stress markers (8-hydroxy-deoxyguanosine and total reactive oxygen species), and inflammatory markers such as high sensitivity C reactive protein, interleukin (IL)-6, and IL-8 in the CC group, while there was no change in the vitamin C group.	CC juice may have powerful anti-oxidative and anti-inflammatory properties, compared to vitamin C tablets containing equivalent vitamin C content.
Studies in animal models				
Azevedo *et al.* [22]	Male Swiss mice	The animals received crude extracts of CC in three concentrations or water by oral gavage /2xd/ 15 days	The CC extracts resulted in significant protection against doxorubicin and 1, 2-dimethylhydrazine in bone marrow, liver, and gut.	CC extract presents antimutagenic action in this animal model.
Anhê *et al.* [8]	High fat/high sucrose (HFHS)-fed mice.	HFHS mice were treated CC.	CC reduced weight gain, fat accumulation and reduced metabolic inflammation. There was an improvement of and insulin sensitivity and protection against hepatic steatosis	CC prevents the deposition of visceral and liver fat due to brown adipose tissue activation and increased expenditure of energy.
Carmo *et al* [23]	Wistar rats	Groups of animals: 1) control, 2) Camu-camu, and 3) submitted to vertical gastrectomy. All groups were submitted to a high calorie and high-fat diet / 8w. After that, groups 2 and 3 received CC extract 1g / kg / day.	The CC group showed a significant reduction in BMI but not in weight. There were no significant changes in blood glucose.	Despite the use of CC to reduce BMI, it was not as efficient as vertical gastrectomy in controlling body weight in Wistar rats.
Becerra *et al.* [24]	Sprague Dawley rats	Animals were divided into 2 groups: a control group, a gentamicin group with induced nephrotoxicity, a gentamicin group that used CC 800 mg/kg/day, a gentamicin group that used CC 1000 mg/kg/day, and a gentamicin group that used CC 1200 mg/kg/day	Animals that received CC showed a gradual increase in kidney weight (directly proportional to the extract dose). The gentamicin group showed an epithelial loss, deep inflammatory infiltrate, and vascular congestion the CC group showed a lower level of damage. CC also resulted in significant nephroprotective activity on the gentamicin-induced nephrotoxicity animals.	Animals that received CC had nephroprotective activity.
Aride *et al.* [25]	Tambaqui (*Colossoma macropomum*)	Animals received different concentrations of CC (15%, 30%, and 45%) with the diet /30d.	Significant increases in glucose, cortisol, proteins, and triglycerides were observed. Animals treated with 15% and 30% of CC gained the best swimming performance,	The use of CC can interfere with the physiological parameters of tambaqui.
Yunis-Aguinaga *et*	Nile tilapia (*Oreochromis*	Animals received CC extract: 0, 50, 100, 250, and 500 mg/kg of	Treated fish showed a significant increase in white blood cells, lysozyme	The use of CC in the diet improves immune

al. [26]	*niloticus*)	the feed. At the end 5 w, animals were inoculated with *Aeromonas hydrophila* in the swim bladder.	activity, burst respiratory activity, and serum bactericidal activity.	response and growth, especially at 500 mg/kg.
De Souza *et al.* [28]	Streptozotocin-induced diabetic rats	Animals received chronic intake of raw extracts of CC.	Oral use of CC raw extracts significantly reduced TC, TG, and lipid peroxidation; increased plasma antioxidant activity, but no effects were seen on glucose metabolism.	The use of CC can lead to improvement of the lipid profile and can increase antioxidant capacity.
Nascimento *et al.* [29]	Wistar rats	The rats were divided into two groups. An experimental group, which ingested 25 ml/day of CC pulp, and an untreated group.	Animals that received CC showed a reduction in adipose tissue, plasma glucose levels, CT, TG, LDL-c, and insulin levels; they also had an increase in HDL-c levels.	The result of the study found that the CC pulp was able to reduce weight loss in rats.
Schwertz *et al.* [30]	Ratus *norvegicus* With dyslipidemia	After induction of dyslipidemia, the animals were randomly divided into 5 groups, and 3 of them submitted to treatment with different concentrations of CC juice (0.4mL.kg-1, 4.0mL.kg-1, and 10mL.kg-1)/14 d; 1 group was submitted to treatment with quercetin (10mL.kg-1) and 1 hyperlipidemic control group.	The results showed that CC and quercetin juice in different dosages leads to a reduction in TC, TG, fecal cholesterol excretion, and hepatic cholesterol reduction.	CC juice helps in the lipid profile of dyslipidemic rats.

CC: Camu-camu; LDL-c: Low Density Lipoprotein; TC: total cholesterol; TG: Triglycerides.

Conflict Of Interest

The authors declare no conflict of interests.

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