Research, Society and Development, v. 10, n. 6, e27810615877, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i6.15877

CAMU-CAMU (*Myrciaria dubia* (HBK) McVaugh), a small Amazonian fruit rich in vitamin C and a supplement for immunity

CAMU-CAMU (*Myrciaria dubia* (HBK) McVaugh), um pequeno fruto rico em vitamina C como suplemento para imunidade

CAMU-CAMU (Myrciaria dubia (HBK) McVaugh), un pequeño fruto rico en vitamina C como suplemento para la inmunidad

Received: 05/07/2021 | Reviewed: 05/12/2021 | Accept: 05/13/2021 | Published: 05/30/2021

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Abstract
The Amazon Rainforest is rich in a diversity of species with various bioactive properties that have been widely used to treat a variety of inflammatory diseases. During the infection process, an oxidative stress environment is created that leads to cellular damage mediated by the transcription factor NF-kB, and triggers the production of pro-inflammatory chemical mediators, such as tumor necrosis factor-α [TNF-α] and interleukins IL-1β, IL-6, which causes a decline in the immune system. In this sense, the camu-camu fruit, which is native to the Amazon region, has in its nutritional composition several bioactive compounds and the highest level of vitamin C among Brazilian tropical fruits. It is also noted for its antioxidant and anti-inflammatory properties. Therefore, the objective of this review is to analyze the evidence collected in the literature regarding camu-camu as a functional food for the immune system in oxidative and inflammatory events.
Keywords: Camu-camu; Immunity; Vitamin C; Antioxidant; Bioactive compounds.

Resumo
A floresta tropical amazónica é rica numa diversidade de espécies com diversas propriedades bioativas que têm sido amplamente utilizados para tratar uma variedade de doenças inflamatórias. Durante o processo de infecção, é criado um ambiente de estresse oxidative o que leva a danos celulares mediados pelo factor de transcrição NF-kB, desencadeando a produção de mediadores químicos pró-inflamatórios, tais como o factor de necrose tumoral-α [TNF-α] e as interleucinas IL-1β, IL-6, o que provoca uma diminuição do sistema imunitário. Neste sentido, o fruto Camu-camu, nativo da região amazónica, tem na sua composição nutricional vários compostos bioativos e o nível mais elevado de vitamina C entre os frutos tropicais brasileiros. Também se destaca pelas suas propriedades antioxidantes e anti-inflamatórias. Portanto, o objetivo desta revisão é analisar as evidencias citadas na literatura sobre o camu-camu como alimento funcional para o sistema imunitário em eventos oxidativos e inflamatórios.
Palavras-chave: Camu-camu; Imunidade; Vitamina C; Antioxidante; Compostos bioativos.

Resumen
La selva amazónica es rica en una diversidad de especies con diversas propiedades bioactivas que han sido ampliamente utilizadas para tratar una variedad de enfermedades inflamatorias. Durante el proceso de infección, se crea un entorno de estrés oxidativo que conduce a un daño celular mediado por el factor de transcripción NF-kB, y desencadena la producción de mediadores químicos proinflamatorios, como el factor de necrosis tumoral-α [TNF-α] y las interleucinas IL-1β, IL-6, lo que provoca una disminución del sistema inmunitario. En este sentido, el fruto del camu-camu, originario de la región amazónica, tiene en su composición nutricional varios compuestos bioactivos y el mayor nivel de vitamina C entre las frutas tropicales brasileñas. También destaca por sus propiedades antioxidantes y antiinflamatorias. Por lo tanto, el objetivo de esta revisión es analizar las evidencias recogidas en la literatura sobre el camu-camu como alimento funcional para el sistema inmune en eventos oxidativos e inflamatorios.
Palabras clave: Camu-camu; Inmunidad; Vitamina C; Antioxidante; Compuestos Bioativos.

1. Introduction

The proper functioning of the immune system is vital for the survival of the individual. This system monitors signs of invasion by harmful substances such as pathogens, innocuous molecules or damage caused by oxidizing agents. Undernourished individuals or individuals with an inadequate intake of certain specific macro and micronutrients that affect and dominate the immune system, for example, the amino acid arginine is essential for the generation of nitric oxide by macrophages (Childs et al., 2019). The effects of certain specific nutrients on the immune system with potential antioxidant action against certain infections and inflammations, mainly those caused by oxidative stress, have been studied by many researchers (Song et al., 2019). A single nutrient can also exert several diverse immune effects, as in the case of vitamin E, which has an inhibitory role of protein kinase C activity, and micronutrients, such as vitamin A and zinc, which regulate cell division, and also vitamin C, which has an important role in antioxidant response in the immune system (Wessels, Green & Beck, 2017).

The European Journal of Clinical Nutrition concluded that "without proper nutrition, the immune system is clearly deprived of the components necessary to generate an effective immune response" (Calder et al., 2020). Therefore, the intake of a diet rich in nutritious foods leads to an optimal functioning of the immune system, since it adds antioxidants with the possibility of delaying or repairing cellular damage caused by free radicals. This contrasts with diets of ultra-processed foods and that are deficient in fruits and vegetables and suppress immunity (Lobo et al., 2010; Cohen et al., 2017; Molendijk et al., 2019)

Recently, several studies of rodents and humans have established that diets that are deficient in certain nutrients are associated with elevated serum inflammation markers, which suggests that the immune system responds directly or indirectly to the existing nutritional pattern (Kuper et al., 2016; Molendijk et al., 2019). Where there are nutritional deficiencies, there may be a greater focus of disease, with longer recovery processes and longer periods fighting illnesses (Borji et al., 2018). In addition to a balanced diet, other protocols with specific nutrients are being used for modulation of the immune system and vitamin C in one case under experimentation. Vitamin C apparently protects and suppresses respiratory and systemic infections of the upper respiratory tract by modulating the immune system (Kuper et al., 2016). In animals with respiratory infection, a protocol of vitamin C intake improved hematosis, increased alveolar fluid cleansing, and modulation of infection occurs through bronchoalveolar epithelium and attenuation of neutrophil retention (Fisher et al., 2012).

However, the choice and intake of certain specific nutrients should be related to the patterns presented by individuals in regards to infections or inflammations. Some individuals do not present infections, while some present infections of mild and moderate form, or infections that develop diseases of severe form, as well as individuals who have overcome the disease.

In cases of individuals who do not present infections and inflammations, the goal of the intake of certain specific nutrients should be to strengthen the immune system before the infection becomes a problem. On the other hand, individuals who have overcome infections or inflammations, depending on their severity, present, among others, a picture of oxidative stress on immunosuppression, excessive loss of lean mass, imbalance between proinflammatory and anti-inflammatory cytokine synthesis and misadjusted antioxidant defenses. In this way, specific nutrients that can reestablish and control these imbalances must be given in these patterns.

In addition to specific supplements, which have attracted the attention of certain researchers, is the intake of bioactive elements, originating, mostly, from plants and their constituents, such as their fruits, stems, seeds, bark and roots, which have the ability to articulate metabolic pathways in the body and increase the immune response against pathogens, infections, inflammation and diseases arising from oxidative stress (Jung et al., 2015; Subashini et al., 2015; Wei et al., 2015; Gombart et al., 2010; Gasmi et al., 2020)

The Amazon Rainforest is endowed with a rich and diverse biodiversity, as well as an extraordinary and extensive genetic plant source. Scientific investigations and certain trials document the potential Amazonian plants and their fruits. Among these fruits is the camu-camu (*Myrciaria dubia* (HBK) McVaugh) which possesses between 2,000 and 6,500 mg in 100 g of

ascorbic acid in its the pulp, and is used as food *in natura* by indigenous and Amazonian riverine populations (Vidigal et al., 2011). Thus, this article aims to increase the visibility of camu-camu (*Myrciaria dubia* (HBK) McVaugh) with regards to the immune system, due its excellent antioxidant activity. This analysis is based on the high content of vitamin C, its nutritional components and bioative compounds when compared with other tropical fruits. These benefits could be of use in individuals with or without the presence of infection or inflammation and who need to increase or modulate their immune system.

2. Methodology

To achieve the objective of this review, papers in Portuguese, Spanish and English were retrived from the Scielo, PubMed and Google Advanced Scholar databases. Initially, a search was carried out on the topics immunity and nutrients, and employed groupings of the keywords “immunity and food”. In the second moment, the grouping was carried out with the keywords "camu camu, diseases, antioxidant, ascorbic acid, phenolic compounds”. The criteria used for the selection of the papers were that they contemplated the theme of immunity and specific nutrients, as well as papers that had relationships with evidence in *in vivo* and *in vitro* research models, the actions or antioxidant and antiflamatory potential of the fruit camu camu. Theses and dissertations, and texts that were not relevant to the study or that did not deal with the topic were excluded. All published papers were peer reviewed between 2010 and 2020. This review followed the methodological proposal indicated by (Pareira et al.,2018)

3. Camu-camu (*Myrciaria dubia* (HBK) McVaugh) and its nutritional characteristics

Variety of plant species, herbs and fruits various active ingredients widely used for treatment of a of diseases. Many fruits, such as cubiu (*Solanum sessiliflorum* Dunal), have been used for treatment of hypercholesterolemic rats (Maia et al., 2015); as well as Crajirú (*Arrebidaea chica* Verlot) in the treatment of anemia (Rodrigues, 2014); tucumã-da-amazônia (*Astrocaryum aculeatum*) for obesity (Leal et al., 2019); acai (*Euterpe oleracea*) in cardiovascular diseases (De Moura Rocha, 2015); guarana (*Paullina cupana*) in atherosclerosis (Seehaber et al., 2016); Taperebá (*Spondias mombin* L.) for the treatment of prostate cancer (Paim, 2019); Murici (*Byrsonima crassifolia* (L.) Kunth for the treatment of inflammatory diseases (Siguemoto, 2013), among others.

Recent trials attest to the high content of vitamin C/ascorbic acid in camu-camu (Grigio et al., 2017) and it is considered among researchers to be the greatest natural source of vitamin C among tropical fruits, with concentrations that can vary between 2,000 and 6,500 mg in 100 g of pulp, and is thus superior to acai (*Euterpe oleracea* Mart.), Cajá (*Spondias lutea* L.), umbu (*Spondias tuberosa* Arruda) and even superior to the levels of vitamin C found in acerola acerola **(*Malpighia emarginata*).** which is considered a superior source of ascorbic acid among tropical fruits (Vidigal et al., 2011).

Camu-camu (*Myrciaria dubia* (HBK) McVaugh) is a small globular fruit with an average weight of 11.7 g, and is commonly found on the banks of the Negro River in the Amazon Rainforest. After harvesting, the fruit has an average of 65.2% pulp, 19.5% seeds and 15.3% peel.

In its nutritional composition, there is a variety of minerals such as sodium, potassium, calcium, zinc, magnesium and manganese (Araújo, 2019); vitamin A, and sugars, such as glucose, fructose, starch, pectin (Akachi et al., 2010). In its protein constitution, different types of amino acids are present, such as serine, valine, leucine, glutamate, proline, phenylalanine, threonine and alanine.

In addition to phenolic compounds, carotenoids and flavonoids, ellagitanins, anthocyanins, cyanidin-3-glucoside, quercetin, myricetin, catechin, xarinic acid and gallic acid, chlorogenic acid, ellagic acid, syngenic acid, and soluble and insoluble fibers have been described in the fruit (De Azevêdo et al., 2014; Ferreira, 2020).

4. Camu-camu (*Myrciaria dubia* (HBK) McVaugh) and its high vitamin C content

Several studies have analyzed the content of vitamin C present in various parts of the fruit. Figure 1 shows the appearance of the camu camu fruit and the chemical structure of vitamin C (ascorbic acid), the main active ingredient of the fruit. In early stages of maturation, ascorbic acid values of 759.02 mg per 100 g to 1,071.12 mg per 100 g were found (Pinto et al., 2013) in the final stage of maturation the values were between 2,010 ± 65 mg.100 g^{-1} FM (Chirinos et al., 2010) to 2,280 ± 65 mg.100 g^{-1} FM. 1,946 per mg/100g (Aguiar et al., 2018).

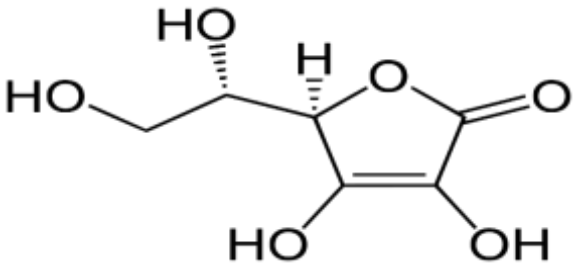
When the fruit was analyzed *in natura*, in the peel of the harvested fruit after 88 days, the concentration was 4752.23 mg of ascorbic acid/100g and in the pulp in the same period 5178.49 mg of ascorbic acid/100g (Arellano-Acuña et al., 2016). In the fruit, after freezing and thawing, Yuyama (2011) and Grigio et al. (2017) obtained 7,355 mg of ascorbic acid 100 g^{-1}, and the values 13,756. 79 mg/100 g for pulp after the freeze-drying process (Neves et al., 2015).

The vitamin C content found in camu-camu is 20 times higher than that of acerola (*Malpighia emarginata*) and 100 times higher than found in lemons (*Citrus limon* (L.) Osbeck) (Myoda et al., 2010). Rufino et al. (2011) described the antioxidant activity of camu-camu using the DPPH method as IC_{50}= 42. 6 g DM.g^{-1}, which demonstrates a positive synergy between antioxidant activity and vitamin C content. Chirinos et al. (2010) using the DPPH method, concluded that ascorbic acid has a share of 70% of the antioxidant capacity of camu camu.

Studies point out that after the pulp is removed from the fruits, it should be refrigerated or frozen as soon as possible, since the active ingredients, such as ascorbic acid, phenolic compounds and other nutrients, can lose their stability. In addition, the pulp can be fermented at room temperature. Thus, the frozen pulp should be kept in a freezer and protected from direct light.

Souza et al. (2011) evaluated the effect of freezing on the physico-chemical characteristics of camu-camu pulp stored for 15 months at -18 ºC. The results indicated that there was no significant difference between the quality of the initial pulp of camu-camu and after 15 months of storage at 18 °C. In another study, the pulp of the green, semi-ripe and ripe fruits was frozen at -18 ºC and physico-chemical analyses were conducted monthly, for four months, an aliquote was removed from the pulps and transformed into juices with refrigeration at 4 ºC for 24 h, with analyses performed at 0 h, 2 h, 4h, 6 h and 24 h.

Figure 1. Camu-camu fruit (*Myrciaria dubia* (HBK) McVaugh) and the structure ascorbic acid.



Source: Adapted from Aguiar et al. (2018).

Vitamin C concentrations for green, semi-ripe and ripe fruits were 26.84 mg/100 g, 20.21 mg/100 g and 27.46 mg/100 g, respectively. During the storage of frozen pulp and chilled juice, there was a slight variation in the initial and final pH values of soluble solids, while the vitamin C content showed a considerable reduction (Silva & Da Conceição Ferreira, 2018).

For this reason, it is recommended that the fruit in the final stage of ripening or when it has a red color be stored at temperatures of about 10 °C in packages of modified atmosphere (Hernández et al., 2011). In addition to the form of freezing, it is important to prevent the degradation of the fruit. Salomão-Oliveira et al. (2016) observed that freeze-dried camu-camu in gelatin capsule is able to create a light barrier, protecting the fruit against oxidation and moisture absorption.

This protection contributes to reduce the degradation of the processed fruit, ensuring the prolongation of the shelf life, as well as the stabilization of the antioxidant components associated with the refrigeration temperature. The storage of the product after analysis of 90 days had an acceptable loss of vitamin C, since ascorbic acid is readily oxidized when exposed to oxygen, light, air temperature, long shelf life and the type of packaging.

In addition, it was found that encapsulation and preservation by refrigeration were paramount to ensure the physicochemical and microbiological quality of the freeze-dried camu camu. During the study, two analyses of vitamin C in freeze-dried fruits were performed. At baseline (t = 0) the estimate of vitamin C was 3.04 g/100 g^{-1} and in the third month (T = 3) it was 2.60 g/100 g^{-1}.

When camu-camu juice is mixed with other fruits or foods, we have the following results. Campos, (2020) observed the stability of vitamin C in the formulation of camu-camu (*Myrciaria dubia*) and jambolan (*Syzygium cumini*) juice during storage at 25 °C. After analysis, the results indicated a degradation of vitamin C after 10 days of storage.

Sarmento et al. (2019) evaluated the stability of ascorbic acid in buffalo milk yogurt with different concentrations of camu-camu pulp during the storage period. The physicochemical characteristics of the pulp and buffalo milk yogurt prepared from two formulations with 8.3% (F1) and 12.5% (F2) of camu-camu pulp were evaluated, in addition to the stability of the ascorbic acid in the product stored under refrigeration (5 ± 1 °C) for 28 days.

The analyzed pulp and yogurt formulations presented physico-chemical characteristics as seen in the literature and recommended by the legislation in force in Brazil. The results indicate that the ascorbic acid content in the formulations was 242.2 mg/100 g (F1) and 317.73 mg/100 g (F2) at D0 and 171.0 mg/100 g (F1) and 242.2 mg/100 g (F2) on D28 of storage, with a 30% loss in ascorbic acid content during the entire storage period these were not superior to camu-camu.

Phenolic compounds function as radical scavengers and sometimes as metal chelators, acting both in the initiation step and in the propagation of the oxidative process (Scheme 1).

Scheme 1. Oxidizing action of flavonoids.

Flavonoids (OH) + R * > flavonoids (O*• + RH

Flavonoids (OCH3) + R * > flavonoids (O•) + RCH3

Source: Adapted from Babu et al. (2013).

Among other active phenolic compounds found in camu-camu are quercetin during the fruit maturation phase with results indicating 38.98-60.75 quercetin equivalent/100 g (Neves et al., 2015), 1120 polyphenols (mg/100 g) (Yuyama, 2011), and a cumulative phenolic compound content of 1420 mg GAE.100 g^{-1}. In the case of ripe fruit, anthocyanins present 21.95 mg/g (Neves et al., 2015) and 1161 mg of GAE/100 g DM (Villanueva-Tiburcio et al., 2010; Akter & Ahmed, 2011).

In their study of the lyophilized product of the fruit, Fracassetti et al. (2013) compared the flavanoid values between whole flour made from camu-camu and powdered pulp, which gave 4,007.95 mg/100 g and 48.54 mg/100 g, respectively.

Recently, Langley et al. (2015) cited Brazilian fruit pulps their analysis, among the fruits camu-camu showed a high content of chlorogenic acid, ellagic acid, quercetin and kaempferol. The authors highlight camu-camu as having the highest content of vitamin C, and total phenolics were responsible for the highest DPPH sequestering activity.

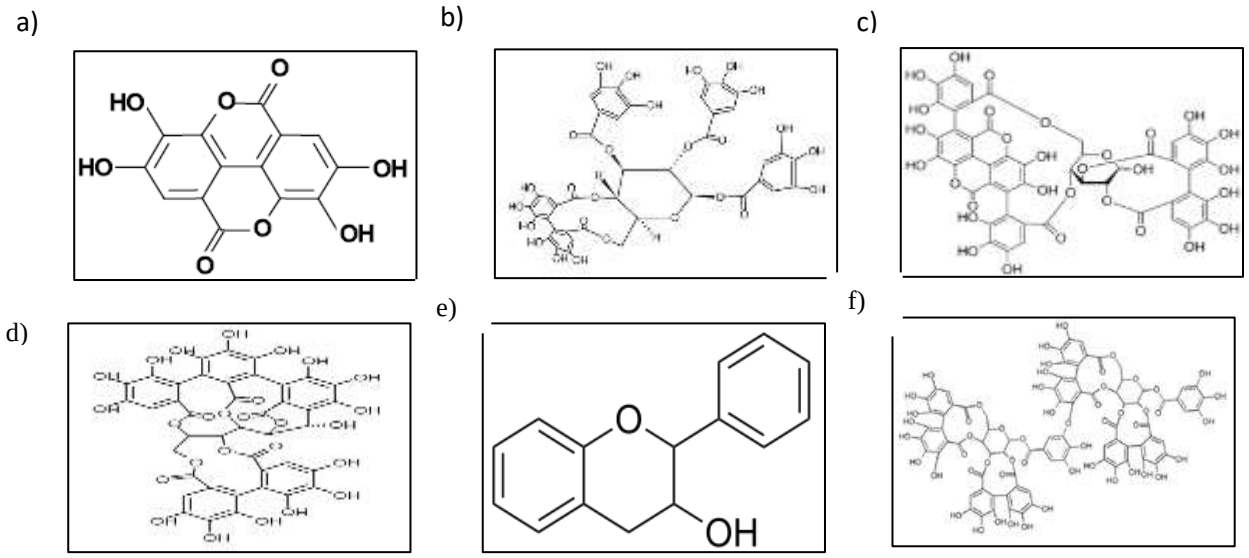
Analyzing the components of the fruit, Bataglion et al. (2015), in studies of the pulp of camu-camu *in natura*, found 40 mg quercetin equivalent/100 g) and, in the dry pulp, they found 1.176 ± 14.8 mg GAE.100 g^{-1} FM. Similarly, Fideles et al. (2019) subjected camu-camu to drying at 60 ºC and obtained 17.93-27.20 mg quercetin equivalent/100 g. Comparing the

bioactive compounds present in the camu-camu with the fruits cubiu (*Solanum sessiliflorum*) and in the purple araçá (*Psidium myrtoides* O. Berg), 732 mg GAE/100 g quercetin equivalent/100 g were found in fresh fruit, which is much higher than cubiu and 12% higher than purple araçá (Rodrigues, 2016). At the end of the study, the author concluded that camu-camu showed values of 732 mg GAE/100 g in fresh fruit.

Kaneshima et al. (2013) state that C-glycosidic elastin, together with ascorbic acid, anthocyanins, cyanidine-3-glucoside, total polyphenols, flavonoids quercetin, myricetin, catechin, xarinic acid and the gallic acid of the seeds of the camu-camu fruit may be responsible for the antioxidant activity of the fruit. After the analysis and comparison of the antioxidant capacity of other Brazilian fruits, such as acerola, jabuticaba (*Plinia cauliflora*), cagaita (*Stenocalyx dysentericus*), açaí (*Euterpe oleracea*), java plum (*Syzygium cumini*), camu-camu is highlighted as having a positive correlation between ascorbic acid and total polyphenols in assays that tested the oxygen radical absorbance capacity (ORAC) (r) = 0. 795; p <0.001) and DPPH (r = 0.989; p <0.001).

In the separation of the active components of camu camu, Langley et al. (2015) and Myoda et al. (2010) noted that the proportion of ascorbic acid (67.5% -79.3%) and the quota of (20.7% -32.5%) of the phenolic compounds present in the peel and seed, which are mainly myricetin, ellagic acid and ellagitanins, cyanidine 3-glycoside, quercetin and proanthocyanidins, have values that are higher than the sum of the skin and the seed of acerola. The authors concluded that the fractional extracts of seeds and peel of camu-camu have a high total phenolic content when compared to other tropical fruits, thus highlighting their antioxidant activities. Chemical structure of other phenolic compounds found in the fruit are shown in Figure 2.

Figure 2. Main phenolic content identified in the fruit camu camu: a) Ellagic acid and its derivatives; b) Telimagrandine II; c) Punicalagine; d) Castalagine; e) Flavano-3-ols; and f) Sanguin H-6.



Source: Adapted from Campos et al. (2020).

5. Antioxidant and Anti-inflammatory Effects of camu camu

In biological systems, the lipoprotein portion of cell membranes live under constant aggression from free radicals, which is known as lipid peroxidation, which affects the fundamental and functional integrity of the cell membrane, and alters the flow and permeability of certain substances (Del Ré & Jorge, 2012). An antioxidant can be determined as any element that, when present in low concentrations interrupts, reduces or prevents the reaction chain of an oxidizable substrate (Murphy, 2012).

This antioxidant can be recognized or found in two ways. Exogenous or non-enzymatic dietary antioxidants (vitamins C and E, β-carotene, Cu, Se, Zn, ubiquinone, carotenoids and flavonoids) with endogenous antioxidants an integrated antioxidant cell network (Handy & Loscalzo, 2012; Patlevič et al., 2016).

Enzymatic antioxidants are represented by superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and catalase (CAT) (Handy & Loscalzo, 2012; Patlevič et al., 2016). The actions of these compounds help to neutralize free radicals, chelate metals and block the action of reactive species, especially those of oxygen.

The inflammatory process encompasses a network of molecular and cellular signals in the passage from acute to chronic inflammation release pro-inflammatory cytokines, such as interleukin IL-1, tumor necrosis factor (TNF), interferon (INF)-γ, IL-6, IL-12, IL18 and granulocyte-macrophage colony stimulating factor. However, the body responds with an action that is antagonized by anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, INF-α and transforming growth factor.

The nuclear transcription factor-kB (NF-kB) regulates the expression of various genes that encode pro-inflammatory cytokines. This disequilibrium of anti-inflammatory pro-inflammatory cytokines causes oxidative processes and leads to various inflammatory diseases, for example, atherosclerosis, neurodegenerative diseases, arthritis, diabetes, obesity, thus causing a collapse of the actions of immunological cells (Brewer, 2011). Castro Gomez et al. (2018), in ethnopharmacological studies involving Amazonian plants, report that the fruit of camu-camu (*Myrciaria dubia* (HBK) McVaugh) can be used in medicinal mixtures to treat various inflammatory diseases caused by oxidative stress. These findings are in research involving both animals and humans (Aguiar & Amaral Souza, 2018: Gombart et al., 2020).

In mice, the pulp initiated genotoxic, antigenotoxic and antioxidant effects with reversal of DNA damage in bone marrow, reduced parameters in experimentally induced obesity, caused hepatoprotective and anti-inflammatory actions, protected pancreatic cells, had success against cardiovascular diseases, showed efficient reduction of lipid peroxidation, and antihypertensive and renal antioxidant efficiency. All of these findings were using rats and the antioxidant and antihypertensive effect was *in vitro* (De Souza Schmidt Goncalves et al., 2010; Yazawa et al., 2011; Da Silva et al., 2012: Schwertz et al., 2012; Becerra et al., 2019)

In humans, the antioxidant and anti-inflammatory effect was described in the study carried out in Japan with 20 male volunteers who were smokers. Half of the group were supplemented with 70 ml of camu-camu juice, and the rest of the group ingested a dose of 1050mg of vitamin C in capsule form. After 7 days of intervention, the markers of oxidative stress (8-hydroxy-deoxyguanosine) in the urine decreased significantly in the camu-camu group, while there was no change in the group that took vitamin C capsules. The author also evaluated the inflammatory markers in this case and the C-reactive protein and interleukins presented expressive reduced values (Inoue, 2008)

Ellinger et al. (2012) created a supplement using the mixture of acai juice, Andean blackberries and camu camu. The randomized, controlled crossover study was applied to 12 healthy volunteers supplemented with 400 mL of the mixture or a placebo solution. In this study, the main objective was to observe the action of the mixture on the total antioxidant capacity in the blood, using the following assays: trolox equivalent antioxidant capacity (TEAC) and Folin-Ciocalteau (FCR). The results indicated that TEAC and FCR were not affected by the drink, despite the mixture having a very high content of ascorbic acid and bioactive substances with reducing properties.

In their research, Nascimento et al. (2013) reported the antioxidant and anti-inflammatory action of camu-camu pulp in a mouse model with experimental obesity. Hypothalamic obesity in the rats was idealized using subcutaneous injections of monosodium glutamate in an *ad libitum* diet. The rats were divided into two groups: an experimental group supplemented with 25 ml of camu-camu pulp per day and an untreated control group. After 12 weeks of intervention, white fat deposits were reduced inflammatory markers and liver enzymes

Yazawa et al. (2011) proved the anti-inflammatory effect of camu-camu seed extract on mice with edema on the hind leg. The extract significantly reduced the creation and swelling of edema. Thus, the author concluded that camu-camu seed extract is a substance that possibly has bioactive components capable of exerting anti-inflammatory effects, in this case, preventing diseases associated with immunity.

Additionally, an oral administration of camu-camu extract was performed to measure immunological parameters in Nile tilapia (*Oreochromis niloticus*). A total of 400 Nile tilapia (80 ± 5 g) were randomly distributed in 20 tanks with a capacity of 1,500 L each (20 fish/tank). Camu-camu extract (containing 40.5 mg of vitamin C/g detected by high efficiency liquid chromatography) was mixed in batches of 0, 50, 100, 250 and 500 mg/kg of feed. Each batch of feed was served to the fish four times a day. At the end of the experimental period, the fish were inoculated with *Aeromonas hydrophila*. Blood samples were taken after 6, 24 and 48 h of inoculation. The results showed that fish supplemented with camu-camu extract showed a significant increase ($p < 0.05$) in white blood cells, lysozyme activity, serum bactericidal activity, direct agglutination and melanomacrophage count. No toxicity was found in the intestine, kidney or spleen of the fish. In conclusion, the addition of camu-camu extract in tilapia ration intensified the immune response after 5 weeks, mainly at a dose of 500 mg/kg.

Fidelis et al. (2020) researched the *in vitro* antioxidant and antiproliferative action of lyophilized camu-camu (*Myrciaria dubia*) seed extract in a yogurt model. The lyophilized portion of camu-camu contained the following phenolics: vescalagine, castalagine, gallic acid, procyanidine A2 and (-) - epicatechin. The camu-camu had its antioxidant activity evaluated by different methods (2,2-diphenyl-1-picrylhydrazyl, Folin-Ciocalteu reduction capacity, total reduction capacity, ferric reduction antioxidant power and CU 2+ chelating capacity), and in this assay the camu-camu extract inhibited cell proliferation of HepG2 cells (human hepatoma carcinoma; CI 50CELLS = 1116 ug/mL) and Caco-2 cells (human hepatoma carcinoma; CI 50cells = colorectal epithelial adenocarcinoma; CI 50 = 608.5 ug/ml).

The *In vitro* camu-camu extract inhibited the action of α-amylase, α-glucosidase, in addition to DNA protection in peroxyl radical-induced fission, copper-induced oxidation of human LDL, and reduced the release of TNF-α and caused activation of NF-kB in macrophage cell culture. The extract mixed in yogurt at concentrations (0, 0.25, 0.5, 0.75 and 1.0 g/100 g) increased antioxidant and chemical reducing capabilities. The authors' conclusion was that camu-camu seed extract may be a potential antioxidant and antiproliferative ingredient.

The same results were conferred by Willemann et al. (2020) using an optimized camu-camu extract for inhibition of the growth of *Listeria monocytogenes, Pseudomonasaeruginosa, Salmonella Typhimurium, Salmonella Enteritidis, Bacillus cereus* and *Staphylococcus aureus*. The extract contained vescalagine, castalagine and 3,4-dihydroxybenzoic acid. In addition, *in vitro* there was inhibition of the enzyme α-amylase, α-glucosidase and angiotensin-converting enzyme, and the extract showed cytotoxic effects for the cancer cells Caco-2, A549 and HepG2, but no cytotoxicity for IMR90 cells. At the end of the study, the authors concluded that the optimized camu-camu extract exerted antioxidant, antidiabetic, antihypertensive and antiproliferative action. In addition, the inflammatory ballast due to infections is related to the expression of the genes TNFalfa, IL-1, IL-8 and ICAM-1, having as its promoter the nuclear transcription factor NF-kB. Table 1 will describe the general aspects of camu-camu (Myrciaria dubia) and table 2 will show in vivo and in vitro studies demonstrating the pharmacological action of the fruit.

Table 1. General aspects of the fruit of camu-camu (*Myrciaria dubia*).

Botanical nomenclature	*Myrciaria dubia* (HBK) McVaugh Botanical Family: Myrtaceae	Ref. [73]
Synonyms	*Myrciaria divaricata* (Bentham) O. *Berg Myrciaria paraensis* O. *Berg Myrciaria spruceana* O. *Berg Psidium dubium* (HBK)	Ref. [73-115]
Common names	Camu-camu, camu-camu negro, caçari, araça, azedinha, algracia, guayabillo blanco, guayabito, limoncillo (Venezuela)	Ref. [73 115]
Geographical Distribution	Brazilian, Bolivian, Colombian, Ecuadorian, Peruvian and Guyanese Amazon	Ref. [73-115]
Plant Material	Studies using leaves, fruits (pulp, peels and seeds); - Bush of 3 m to 8 m in height; - Edible fruit, sour taste, pink pulp, spherical fruit with a diameter of 1-3 cm, ripe with reddish-brown to black-purple coloring; - Seeds 8-5 mm long and 5.5-11 mm wide, one to three units, noticeably flattened and covered by a network of fibrils.	Ref. [73-115]
Pharmaceutical formulation: lyophilized or atomized Pulp	Vitamin C capsules or tablets, collagen inducer.	Ref. [98 111, 114]
Pulp food industry	Drinks: liquor, beers. Foods: cereal bars, flours, animal feed, yogurt, blends, cheese, milk, candied fruit, jelly/jam, popsicles, candy, cookies	Ref. [98 111, 114]
Health promoting properties	Anti-anemic activity, anti-inflammatory activity, healing activity, antiplasmodic activity, antigenotoxic activity, anti-obesity activity, neuroprotective activity, antidiabetic activity, antimicrobial activity, cell antiregeneration activity and hepatoprotective activity	Ref. [26,29,33,36,38,62,73,75, 78,79,81,96]
Micronutrients and macronutrients with pharmacologic activity identified in seed pulp and peel	Ca, Mn K, Mg), Fe, Zn, Al, B, Br, Cr, Mo, Se, Cu, Na, P, K, S, B, Fe, Na, Se, Co, Cl. Vitamin C, niacin, riboflavin, thiamine,	Ref. [27-36,73]
Amino acids with pharmacologic activity identified in seed pulp and peel	Valine, leucine, threonine, serine, glutamate, proline, phenylalanine, threonine, alanine, aminobutanoate	Ref. [35-38,73]
Bioactive substances identified in seed pulp and peel	Anthocyanins (delphinidine 3-glycoside and cyanidine 3-glycoside), translutein, lutein, beta-carotene, zeaxanthin and neoxanthin, morin, rutin, kaempferol, quercetin, myricetin, catechin, epicatechin, xarinic acid and gallic acid, chlorogenic acid, ellagic acid, syngic acid, caffeic acid, ferulic acid,	Ref. [61,62-64,73,75,-77,80]
Fatty acids with pharmacologic activity	C18: 3ω3 (α-linolenic); C18:2ω6 (linoleic); 5Ω3 (EPA); tridecanoic acid; palmitic acid; stearic acid; oleic acid; eicosadienoic acid; tricosanoic acid.	Ref. [31,43,44,73]

identified in seed pulp and peel		
Traditional Use	Asthma, arteriosclerosis, cataracts, depression, flu, gingivitis, glaucoma, hepatitis, infertility, migraine, osteoporosis and Parkinson's disease.	Ref. [73-115]
Adverse effects	There are no known adverse effects and/or contraindications from ingestion of the fruit or camu-camu residues.	Ref. [63,73, 115]

Source: Authors.

Table 2. *In vitro* and *in vivo* studies reporting the biological properties of different parts of camu-camu (*Myrciaria dubia*).

Model	Fruit residues	Assay/Dose	Result	Ref
In vivo	Pulp	Experimental obesity in Wister rats: the experimental group ingested 25 mL/day of camu-camu pulp for 12 days, while the placebo group received distilled water.	After 12 weeks, the animals that received the pulp: ↓ BMI; ↓white adipose tissue deposits.	[26]
In vivo	Pulp	Experimental obesity in Wister rats: divided into sedentary group S (untreated), exercise Group E (continuous swimming training), camu-camu Group C (25ml camu-camu pulp/day) and exercise and camu-camu EC (25ml camu-camu pulp/day + continuous swimming). The experiment lasted 12 weeks.	After 12 weeks, the camu-camu group obtained the following results: ↔ TC, TG, ↓ glucose and ↑ HDL-C and in relation to the investigated groups, except in the control group.	[116]
In vivo	Pulp	Wistar rats with experimental dyslipidemia randomly divided into 5 groups (n = 8), 3 of which underwent treatment with different concentrations of camu-camu juice (0.4 mL.kg^{-1}, 4.0 mL.kg^{-1} and 10 ml.kg-^{1}) for 14 days, 1 group underwent treatment with quercetin (10 ml.kg^{-1}) and 1 hyperglycemic group.	Doses of camu-camu juice and quercetin showed lipid profile effects ↻; ↓TG; ↓TC; ↓FC; ↓HC.	[77]
In vivo	Camu-camu capsule	18 volunteers of both genders divided into two groups: 1) intervention group, which received daily capsules of camu-camu containing 320 mg of vitamin C; 2) the intervention, which occurred for 15 days	↓ HDL-C; ↓ TC ↓FG in the camu camu group	[98]
In vivo and *in vitro*	Crude Hydroalcoholic peel extract	Assay involving neoplastic cells of the lines of acute monocytic leukemia (THP-1) and chronic myeloid leukemia (K562). *In vivo*, Swiss females underwent induction of an Erlich ascitic tumor and were distributed in 2 groups of 8 animals. One of the groups received treatment with a hydroalcoholic extract, by gavage, in the concentration of 1g of extract per kg of animal weight.	↑ anti-inflammatory and protective effect for tissue injury	[117]
In vivo	Pulp	The biological assay was performed in Wistar rats treated with 2.5 mL of a camu-camu shake, commercial shake reconstituted in skimmed milk, and a placebo group treated with water via gavage for a period of 28 days	↔ glucose; ↓ TC; ↻ BMI.	[118]
In vivo	Crude camu-camu extract	Obese rats received oral doses (200mg/kg) of raw camu-camu extract, while the untreated group received distilled water and vitamin C (6.6 mg/kg) over 8 weeks.	↓ body weight; ↓glucose and insulin ₱ hepatic steatosis; ↑ caloric expenditure; increased energy expenditure↑ mRNA	[96]

			expression in brown adipose tissue (BAT)	
In vivo	Seed extract	Mice with models of paw edema induced by carrageenan, ingested 1000 to 2000mg/Ml of camu-camu extract for seven days.	↓ formation of edema; ↑ release of nitric oxide from raw 264.7 cells derived from macrophages *in vitro*.	[75]
In vivo	Pulp extract	Diabetic animals were divided into two main groups. TI: diabetic rats received a dose of 1 g/kg of water. Camu-camu extract of frozen pulp by gavage for 30 days; TII: diabetic rats received a dose of 3 g/kg of aqueous pulp. Extract of frozen pulp of camu-camu by gavage for 30 days.	Camu-camu group: ↑ antioxidant activity of plasma, ↓ TG and TC and lipid peroxidation in plasma.	[58]
In vivo	Lyophilized pulp (capsule)	Diabetic individuals divided into two groups: experimental (EG) (n=29) and control (CG) (n=29). The EG Group received one capsule containing camu-camu, containing approximately 442 mg of vitamin C for 45 days, and the CG received one capsule (placebo) during the same time period	There was a significant reduction in some diagnostic indicators of MS, such as ↓ DBP, ↓TG, abdominal circumference and ↓HDL-C.	[43]
In vivo	Pulp extract	Rats with experimental hyperlipidemia and Type 2 diabetes The experimental group received *Myrciaria* (camu camu) 0.6 g/kg for 30 days.	The experimental group: ↓TC, ↓LDL-C and ↓TG and ↑ HDL-C	[119]
In vivo	Alcoholic extract of the camu-camu peel	A gentamicin-induced nephrotoxicity model in rats divided into White Group (B): intraperitoneal saline solution (IP) at a dose of 2 mL/kg. Gentamicin Group (G): gentamicin via IP at a dose of 120 mg / kg. Group 1 (E1) extract: *Myrciaria dubia* (Camu Camu) alcoholic extract at 800 mg/kg orally (PO) and gentamicin via IP at 120 mg/kg. Group 2 (E2) extract: *Myrciaria dubia* (Camu Camu) alcoholic extract at a dose of 1000 mg/kg PO and gentamicin via IP at a dose of 120 mg/kg. Group 3 (E3) extract: *Myrciaria dubia* (Camu Camu) alcoholic extract at a dose of 1200 mg/kg PO and gentamicin via IP at a dose of 120 mg/kg.	The results showed ↓C, in the groups protected with camu-camu alcoholic extract in relation to the gentamicin group ($p < 0.05$). The groups that received camu-camu presented ↑ gradual weight of the kidneys in direct relation to the dose of the extract ($p < 0.05$). Histological analysis showed epithelial loss, intense inflammatory infiltrate and vascular congestion in the gentamicin group, while the groups that received camu-camu with the extract ↓ the severity of the damage.	[120]
In vivo	Aqueous extract of the camu camu fruit	Six groups of six Holtzman rats, five groups with cholesterol-induced hypercholesterolemia were used: positive control group; standard in group three doses of 50, 250 and 500 mg/kg of extract, respectively, and one group without hypercholesterolemia (negative control). The treatment lasted 10 weeks	The results showed a ↓ TC in rats with hypercholesterolemia that consumed the dose of 250 mg/kg in relation to the positive control group (reduction of 21.56%) with a significant difference of $p < 0.002$, no ↔ was observed for HDL. The results, obtained in the determination of antioxidant activity by the DPPH method, show that the inhibitory concentration values 50 (IC_{50}) for trolox is 1.42±0.02 µg/mL	[121]

			and for the extract is 32.22±1.5 µg/mL. At higher doses of camu-camu 500 mg/kg a value of 0.50 E-07 ± 0.21 E-08 is observed, compared to atorvastatin ranging from 3.94 E-07 ± 7.14 E-08.	
In vivo	Lyophilized camu-camu	To evaluate the hypoglycaemic effect of camu-camu in Holtzman rats with Type 2 diabetes (MD2). The sample was divided into two groups; the experimental group received camu-camu at 0.6 g/kg by gavage for 30 days.	The difference between blood glucose levels was significantly greater in the experimental group than in the control group. Conclusion: camu-camu had a hypoglycemic effect in rats with MD2.	[122]
In vivo	Pulp juice	The objective was to determine the effect of camu-camu fruit on 1,2-dimethyl hydrazine-induced colorectal cancer (DMH) in *Rattus norvegicus* var. *albinus*. The control group was exposed to the carcinogen, 1,2-dimethyl hydrazine (DMH) for 21 weeks. For the preventive group, camu-camu juice was administered orally every day in the morning for 7 days and then, from the eighth day onwards, a dose of 874 mg/200g of body weight was administered. The carcinogen DMH was administered once weekly for 21 days and the duration of treatment with camu-camu was 32 weeks. After treatment, the groups were sacrificed for colon removal and pathological examination.	The results show that the preventive group, compared to the control group, showed a slight inflammation, and that despite having administered the carcinogen, there was no greater inflammatory response or progression to damage and/or important structural changes, which is evidenced in the control group; this protection is attributed to oral consumption of camu-camu juice.	[123]
In vivo	Pulp juice	23 healthy subjects were selected to consume seven meal tests, with an interval of 1 week between them, consisting of 50 g of white bread plus 300 ml of water (control) or clarified fruit juice of camu-camu and jaboticaba.	The results indicate that the juices of native Brazilian fruit can be considered as adjuvant treatment for the reduction of postprandial blood glucose.	[124]

↔, no difference; ↑, increased; ↓, reduced; modulation; UI, prevention; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FC, fecal cholesterol; HC, hepatic cholesterol; G, blood glucose; FBG, fasting blood glucose; GOT, glutamic oxalacetic transaminase; DBP, diastolic blood pressure; C, creatinine. Source: Authors.

6. Camu-camu (*Myrciaria dubia* (HBK) McVaugh) as nutritional supplement

Reviewing the literature, evidence emerges indicating that camu-camu exerts a potential effect against anti-inflammatory actions mediated by antioxidants, such as a high content phenolic compound, among them, chlorogenic acid and ellagic acid, and among the flavonoids quercetin and kaempferol, which can increase and preserve a balanced immune response.

Another use for camu-camu would be as a natural alternative to daily vitamin C support and a non-pharmacological option. Secondly, in addition to the pulp and juice, all residues were used in research in humans and animals, thus subsidizing the potential and antioxidant action, anti-inflammatory, antigenotoxic, antiobesity, hypertensive, liver protection and in the prevention of diseases related to the immune system. Thirdly, despite new studies being necessary, the literature provides information and evidence that the camu-camu fruit can be used not only a vitamin C supplement, but as a therapeutic alternative in the form of a dietary supplement in different stages of diseases. Two studies indicate the activity of camu-camu pulp and seed extract in anti-inflammatory support. Yazawa et al. (2011) used camu-camu seed extract, while Da Silva et al. (2012) highlighted the action of camu-camu pulp.

In the trial of Yazawa et al. (2012), the authors analyzed the anti-inflammatory action of methanolic extract of camu-camu seeds in edema lesion after the administration of carrageenan injection in the paw of mice. After 4 hours, the control rats received an oral treatment with dexamethasone (1.0 mg/kg), while the camu-camu groups with lesion demonstrated the following results in calculation of mean and standard deviation in a dose-dependent manner 35.7% ± 6.7% at 2,000 mg/kg, 63.8% ± 7.3% at 1000 mg/kg and 85.1% ± 10.3% at 500 mg/kg. These results were obtained 2 hours after the carrageenan injection. When the extract was tested *in vitro*, there was inhibition in nitric oxide production from RAW 264.7 cells derived from the *in vitro* macrophages. After analysis of the extract, triterpenoid betulinic acid was identified, which is a potent anti-inflammatory substance.

The research of Da Silva et al. (2012) observed the antioxidant, genotoxic and antigenotoxic action of camu-camu pulp on the blood cells of mice. After evaluation of vitamin C per 100 mL of camu-camu, the sample result was 52.5 mg. *In vitro* antioxidant activity evaluated by the DPPH assay in alkaline comet assay was used to analyze genotoxic and antigenotoxic activity. The results indicated that no concentration of camu-camu tested exerted any genotoxic effect and a significant antigenotoxic effect was noted. After the treatments, there was no evidence of toxicity or death in the blood cells.

7. Camu-camu (*Myrciaria dubia* (HBK) McVaugh) and immunity

Given the increase in research using nutrients that increase the immune response, nutritional supplements appear as a viable alternative, since the nutritional status has a fundamental role in the immune action. Foods with essential macro and micronutrients, in addition to bioactive compounds, present in plants, seeds, peels and fruit pulp, have the ability to modulate metabolic pathways in the body, thus enabling the fight against pathological agents, while or at the same time speeding up the recovery of the individual in the case of certain diseases (Helieh, 2017).

In this perspective, bioactive compounds, present in the form of caroteoids, phenolic compounds, micronutrients and vitamins A, C, D, E, B6, B12 and folate as promoters of improvement in the immune response, due to their high antioxidant and anti-inflammatory potential fight diseases and improve health and quality of life (Aslam et al., 2017).

The studies presented so far suggest that camu-camu could be a viable anti-inflammatory option and a powerful antioxidant. This has been established in disease prevention and health promotion by several studies, *in vivo* and *in vitro* (Myoda et al., 2010; 75 Yazawa et al., 2011; Nascimento et al., 2013; Gonçalves et al., 2014).

Infections and inflammations in cases of greater severity lead the body to respond to an inflammatory process with an inflammatory cascade characterized by the actions of cytokines, mainly interleukins (IL-1B, IL-2, IL-6) and tumor necrosis factor (TNF). This imbalance between anti-inflammatory and pro-inflammatory cytokines can occur even after the individual has received medical discharge.

Trials conducted by Fideles et al. (2020) using the atomized extract of camu-camu seed inhibited induced oxidation and, *in vitro*, reduced the release of TNF-α and activation of NF-kB in macrophage cell culture. The may lead to the hypothesis of an antioxidant and anti-inflammatory action of camu-camu due to the high content of ascorbic acid and phenolic compounds, anthocyanins, carotenoids, among others (Grigio et al., 2017). These compounds act on reactive oxygen and nitrogen species, increasing immunity, regulating cell synthesis and degradation and modulating the levels of certain catabolic hormones (Babu et al., 2013). An important factor of camu-camu is the high content of vitamin C found not only in the fruit, but also in its resides.

Preclinical studies using knockout Gluo mice show the modulating impacts of vitamin C on cytokine synthesis. These vitamin C deficient animals infected with the influenza virus in the lower respiratory tract (Kim et al., 2013; Mohammed et al., 2013) had increased synthesis of pro-inflammatory cytokines and decreased synthesis of the inflammatory cytokines TNF-α and IL-1β by isolated neutrophils, respectively. In another trial using septic mice that applied 200 mg/kg of parenteral vitamin C, the mice exhibited reduced synthesis of the inhibitory cytokines TGF-β and IL-10 by Tregs, in addition to moderate elimination of

IL-4 and increased sexcretion of IFN-γ, which is an indication of the immunomodulatory action of vitamin C in sepsis (Gao et al., 2017).

In addition, camu-camu contains the mineral potassium (Araújo, 2019), which increases the *in vivo* availability of vitamin C. This availability has been proven in the research of Ellinger et al. (2012) using a mix of tropical and red fruits with a mixture of 400 ml of camu-camu juice.

This mixture increased the levels of vitamin C in the plasma of 12 participants, when compared to the control group. It has been proven that, depending on the time of harvest, when camu-camu has a red color, the content of total phenolic, anthocyanin and vitamin C increases, thus increasing the antioxidant and anti-inflammatory activity of the fruit (Zillo et al., 2019).

Camu-camu can potentially play a role in integrative therapeutic approaches as a dietary supplement, mainly due to the presence of the high content of vitamin C and its bioactive compounds. Vitamin C is an important enzyme cofactor that influences genes that participate in immunomodulatory function and its effects (Young et al., 2015). Vitamin C encourages neutrophil migration, phagocytic evolution, as well as protection of excessive lesions of infected tissue, increasing neutrophil death, macrophage extraction, as well as proliferation of T and B lymphocytes.

Thus, vitamin C has an important role in helping the immune system to develop and maintain an appropriate result (Berger, 2015; Carr & Maggini, 2017). In addition, tropical fruits including camu-camu, may have an anti-inflammatory and immune action in humans (Mahiunddin, 2010). *In vitro*, animal and human studies including camu-camu juice, even in their experimental stages, are providing references on the impacts as well as the implications on health and in the condition of certain diseases.

In addition to the evidence of antioxidant anti-inflammatory actions of the fruit and its residues, trials and many other supplementary studies have been applied including the use of obese individuals and their comorbidities (Kaneshima et al., 2013; Langley et al., 2015; Arellano-Acuña et al., 2016; Fidelis et al., 2019; Kerimi et al., 2019). This should deserve attention, since many of these diseases reveal a high oxidizing and inflammatory process.

Ellinger et al. (2010) created a mix of fruits added to camu-camu juice that reduced oxidative stress in obese smokers. Vargas (2012) performed an intervention in 18 volunteers: 1) camu-camu group, which ingested a capsule 260mg freeze-dried camu-camu daily during 15 days; 2) control group, which was supplemented was a capsule of 320 mg of synthetic vitamin C. At the end of the research period, the group significantly reduced glucose levels. The authors concluded that insulin levels in the blood led to a stabilization of the weight of individuals.

In the study by Carmo et al. (2019), twenty-four Wistar rats were submitted to obesity induction through a hyperlipidic diet for eight weeks, and were then randomized into three groups: Control Group (CG), Camu-Camu Group (CCG) and Bariatric Surgery Group (BSG). After this period, all animals returned to the normal diet and the intervention period began: CG did not undergo any intervention other than returning to the normal diet; CCG animals were given hydroalcoholic extract of camu-camu, 1g/kg /day, for four weeks by gavage; and the BSG was submitted to the surgical procedure of vertical gastrectomy.

The results indicated that the weight of the animals in the CG increased, and the BSG showed a significant reduction in weight and BMI ($p < 0.05$), while the CG showed a significant reduction in BMI ($p < 0.05$). Moreover, Nascimento et al. (2013) supplemented obesity-induced rats daily with 25 mL of camu-camu fruit pulp for 12 weeks. At the end of the trial, there was a significant reduction in body weight and white fat tissue. Schwertz et al. (2019) used a hyperlipidic diet in Wistar rats and, after supplementation with camu-camu juice (0.4-10 mL/kg) for 2 weeks, the animals showed a reduction in triacylglycerols, total cholesterol and hepatic and fecal cholesterol. The fruit induced the reduction of body weight, visceral fat and the elimination of lipids in the stool and liver showing, in other words, hypolipidemia caused by camu camu.

The studies presented so far suggest that camu-camu could be a viable option with antioxidant effects that is established in disease prevention and health promotion by several studies. *In vivo* and *in vitro* evidence affirms, in addition to the fruit, that the peel and seeds present antioxidant and anti-inflammatory action (Akachi et al., 2010; Myoda et al., 2010; Akter et al., 2011; Aguiar et al., 2018; Sarmento et al., 2019; Campos et al., 2020; Fidelis et al., 2020).

Thus, camu-camu presents potential for new research. The first hypothesis is the antioxidant and anti-inflammatory action due to the high content of ascorbic acid and bioactive compounds, in addition to its nutritional composition. These compounds act on reactive oxygen and nitrogen species, increasing immunity, regulating cell synthesis and degradation, as well as modulating the levels of certain catabolic hormones. These actions reduce the incidence of inflammation.

Another hypothesis to be discussed is the importance of diets rich in fiber and how they can help in the prevention of obesity. In this case, the fruit camu camu has a good portion of dietary fiber in its nutritional composition, which would be an advantage in the control of body weight (Nascimento et al., 2013)

Foods rich in fiber, with phytochemical and antioxidant properties, including camu-camu extract, reduce weight gain, alter inflammations associated with high-fat diets, as well as promote the growth of certain intestinal microorganisms (Anhê et al., 2019). Dietary fibers in addition to regulating energy intake, control satiety, increase the food bolus and are rich in β -glucans.

Murphy et al. (2020) used an *in vitro* lung injury model to study the β-glucan activity of the Shittake mushroom. The authors used 1.5-10 mg/mL of β-glucans. After the experiment, there was a reduction in inflammation with reduced cytokine production, oxidative stress, necrosis and apoptosis, suggesting potential for improvement through a role in preventing cytokine storm.

Although not yet studied, β-glucans from other food sources could result in similar responses, for example, β-glucans derived from algae (in a diet of 108 mg/kg) has been shown to improve the immune responses of weaned pigs experimentally infected with an *E. coli* pathogen. In particular, supplementation of β-glucans reduced tumor necrosis factor (TNF-α), cortisol and haptoglobin ($p < 0.05$) in blood and the expression of various immune genes (IL1B, IL6).

Although there are theoretical approaches and hypotheses about the capacity of plant secondary metabolites, many of these have not yet been justified in clinical trials. The evidence discussed and exposed indicate that camu-camu may be a viable possibility for increasing and modulating the immune response, thus minimizing the anti-inflammatory processes through its antioxidant actions.

Furthermore, at this point, science seeks therapies that will increase immunological status. As such, it would be important, based on the evidence, to verify the potential of the camu camu, through its biochemical and nutritional properties, and its recognizable profile of the vitamin C. We are not asking for all the required steps of scientific research to be excluded, but more applications in human studies, especially before the process of infection, or after discharge of the patient would be beneficial.

8. Final Considerations

In this review, the studies indicate evidence for the role of camu-camu with potential for the increase and modulation of the immunologic system through antioxidant action, with no report of adverse effects through fruit intake and drug interactions in humans.

The fruit can be processed in various ways, and can be consumed in the form of juice, jams, liquor, cookies, yogurt and ice cream. All the residues of the fruit are taken advantage of and this can increase the options in research and exploitation of the fruit in new technologies. Due to the ease in obtaining the fruit, its intake can be daily. Several researchers describe the nutritional content of camu-camu fruit as a substantial source of minerals, fiber, sugars, amino acids, organic acids and fatty

acids, various volatile compounds, polyphenols, and that it presents the highest content of vitamin C among tropical fruits, which qualifies its antioxidant and anti-inflammatory capacity.

Thus, since it is a natural product with the feasibility of being transformed into dietary supplements, it can be used in dietary protocols before the infection occurs or after the infection. The literature also shows that the antioxidant potential of camu-camu was well established through several biochemical studies that indicate in its nutritional composition the potential of the phytochemicals presents in the fruit.

This was tested in animal models and randomized clinical trials in its association with diseases having, among other factors, inflammation and oxidative stress. These tests indicate an antioxidant proportionality between pulp, peel and seeds, which increases the versatility of the fruit.

Since infections and inflammation directly affect the immune system, and knowing that the intake of specific nutrients in the diet affects the immune system, nutritional status is an important factor in strengthening and modulating immunity and thereby counteracting the action of stressors. Thus, the evidence described in this review points that future research can be planned and applied with the camu camu fruit, specifically as a food that can enhance or regulate our immune system.

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