Chapter 5

Myrciaria dubia "Camu Camu" Fruit: Health-Promoting Phytochemicals and Functional Genomic Characteristics

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Abstract

Camu camu is a typical Amazon native fruit shrub that possesses a diploid genome, moderate genetic diversity, and population structure. The fruits accumulate several essential nutrients and synthesize L-ascorbic acid (vitamin C) in great quantities and an array of diverse secondary metabolites with corroborated *in vitro* and *in vivo* health-promoting activities. These beneficial effects include antioxidative and antiinflammatory activities, antiobesity, hypolipidemic, antihypertensive and antidiabetic effects, DNA damage and cancer protection effects, and other bioactivities. Many health-promoting phytochemicals are biosynthesized in several metabolic pathways of camu camu. Their reconstruction from the fruit transcriptome database was accomplished by our research group. These include basic metabolic pathways such as glycolysis and pentose phosphate pathway, vitamin C biosynthesis pathways, and pathways involved in secondary metabolites production. Due to their agronomic potential and fruits growing demand, recently, based on an ideotype, programs were initiated for their domestication and genetic improvement, but so far with very negligible achievements. Consequently, we propose new strategies to accelerate the processes of domestication and genetic improvement based on state of the art technologies for multiomic data analysis and innovative molecular tools.

Keywords: genetic diversity, health-promoting phytochemicals, phenolic compounds, transcriptome, vitamin C

1. Introduction

Myrciaria dubia Kunth (McVaugh) "camu camu" is a typical native Amazonian fruit shrub that thrives in areas exposed to periodical flooding on the banks of rivers, streams, lakes, and swamps

of several Amazonian countries [1, 2]. This plant species possesses a diploid genome, and their genome size (∼230 Mb) is in the range of other Myrtaceae species [3–6]. Populations exhibit moderate genetic diversity and genetic structuring [7–11]. Camu camu produces several essential nutrients such as amino acids, polyunsaturated fatty acids, B-complex vitamins, and high quantities of vitamin C [2, 12–15]. Additionally, the fruits (including peel, pulp, and seeds) and several other tissues/organs (leaves, roots, etc.) accumulate numerous health-promoting phytochemicals with powerful antioxidant, antiinflammatory activities, antiobesity, hypolipidemic, antidiabetic effects, DNA damage and cancer protection effects, hepatoprotective properties, and other beneficial effects [16–24]. These bioactive phytochemicals, in addition to vitamin C, are secondary metabolites that primarily include various phenolic compounds, carotenoids, terpenoids, and several other bioactive metabolites. These associated beneficial effects of phytochemicals were corroborated by numerous *in vitro* and *in vivo* studies with several animal models (i.e., flies, mice, rats, etc.) and human volunteers [16, 17, 22, 24–28]. In the health-promoting phytochemicals section of the book chapter, we will illustrate the chemical structures of several of these phytochemicals that were isolated from various tissues of camu camu by bioassay-guided approaches. These secondary metabolites were biosynthesized in several metabolic pathways of camu camu. In the functional genomic characteristics section, we have presented the reconstruction of some metabolic pathways from the fruit transcriptome database that was accomplished by our research group. These include, for example, basic metabolic pathways (i.e., glycolysis, pentose phosphate pathway), vitamin C biosynthesis pathways, shikimate pathway, and pathways directly involved in secondary metabolites production (i.e., anthocyanins, carotenoids, flavonoids, phenylpropanoids, and terpenoids biosynthesis pathways). Finally, we have included a section about domestication strategy and genetic improvement efforts, where we examine the strategies implemented by Peruvian Institutions to achieve these goals. We have also proposed new strategies to significantly accelerate the domestication and genetic improvement of this species based on the state of the art technologies for multiomic data analysis and innovative molecular tools.

2. General description

2.1. Geographical distribution

Camu camu is a typical native shrub from the tropical rainforest of the Amazon. Wild populations of this species grow in dense areas exposed to periodical flooding (complete submergence for 4–5 months) on the banks of rivers, streams, lakes, and swamps of Guyana, Venezuela (Casiquiare Oreda, Pargueni, Caura, and Orinoco), Colombia (Putumayo and Inirida), Ecuador, Brazil (Trombetas, Cachorro, Mapuera, Maçangana, Urupa, Javari, Solimões, Madeira, and Negro), Peru (Amazonas, Curaray, Itaya, Nanay, Napo, Putumato, Ucayali, Marañon, and Tigre), and Bolivia (**Figure 1**) [1, 2]. In Peru, wild populations only exist in the Loreto Region, consisting of approximately 1345 ha [29], whereas artificial plantations have been established in the Regions Loreto (∼6475 ha), San Martin (∼110 ha), and Ucayali that consist of approximately ∼5930 ha [29–32].

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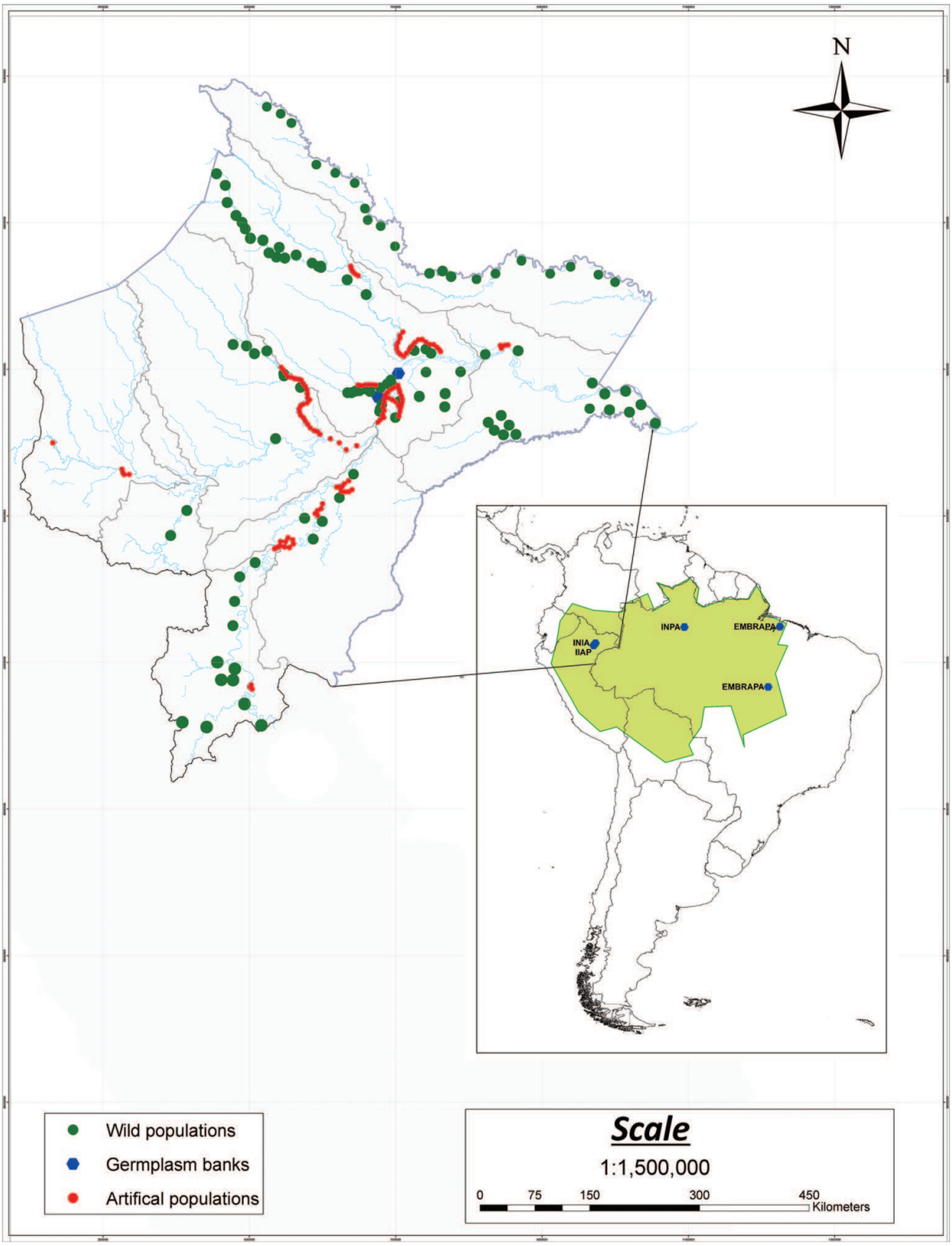

Figure 1. Geographical distribution of camu camu in South American and the Peruvian Loreto region.

2.2. Botanical characteristics

Typically, the camu camu shrub achieves a height of 4–8 m, branching from the base to form several secondary stems, which in turn branch out as an open vessel. The trunk and branches are glabrous, cylindrical, and smooth, and the bark is light or reddish brown, which peels off naturally in periods of drought [14, 33]. The deep-rooted shrub contains numerous absorbing roots. The leaves are opposed, single, petiolar, elliptic-lanceolate (ca. 3–12 × 1.5–4.5 cm), with acuminated apex and oval base, with primary and secondary veins (18–20 pairs). Petioles that are cylindrical have a length of 3–9 × 1–2 mm [34]. The inflorescences are axillary with 1–12 (generally four) subsessile and hermaphrodite flowers arranged in two pairs on the axis. The rounded ciliated bracts and bracteoles are persistent. The calyx is approximately 2 mm long and 2 mm wide and includes four sepals with broad apex and the hypanthium is prolonged and circumscissile at the summit of the ovary and falls with the calyx as a unit after anthesis [35]. The corolla has four white ovate petals which are 3–4 mm long with a ciliated margin. The ovary is inferior with a simple style that is 10–11 mm long, and the androecium has 125 stamens of 6–10 mm in length and anthers of 0.5–0.7 mm length. Although camu camu flowers are hermaphrodite, inbreeding is largely prevented by the lack of synchrony between the development of the gynoecium and androecium, leading to facultative allogamy [14, 33, 36]. The fruits are globular and measure 1.0–5.0 cm in diameter, and their weight averages 11.7 ± 1.4 g [34]. Based on the fresh weight, the fruits are comprised, on an average, of 65.2% pulp, 19.5% seeds, and 15.3% peel [34, 37]. The shiny peel can be pink to deep red or even black when completely ripe, with slightly pinkish pulp [2, 14, 33]. The seeds are kidney-shaped to ellipsoid, flattened bilaterally and are exalbuminous. The fruit contains one to four seeds with an average length of 13.5 ± 1.6 and width of 4.8 ± 0.6 mm. The average fresh seed weight is 440 ± 170 mg. The elongated seed coats are brown and thin and are covered with spiny-celled villi (**Figure 2**) [38, 39].

2.3. Nutritional composition

Pioneering work on the high L-ascorbic acid (vitamin C) content of camu camu fruits was published in 1964 [15]. In this report, the authors indicate that camu camu fruits are among the highest natural sources of vitamin C. Approximately 30 years later, these observations were corroborated by several investigations on the chemical and nutritional composition of camu camu [2, 12, 13, 34, 37, 40–44]. These findings from approximately 60 years of camu camu research are consolidated in **Table 1**. These fruits are composed of nutrients such as protein, carbohydrate, lipids, ash, and crude fiber. Additionally, they have essential amino acids (valine, leucine, phenylalanine, etc.), essential fatty acids of the families omega 3 and 6, vitamin C, and vitamins of the B-complex and several essential minerals for human nutrition, such as potassium, phosphorous, sulfate, calcium, magnesium, cobalt, iron, and several others.

2.4. Chromosome number and genome size

Some standardized karyotype analyses conducted on meristematic cells from root apices have demonstrated that camu camu is a diploid plant with 2n = 22 chromosomes [3, 4], which is consistent with several other Myrtaceae species (i.e., *Acca sellowiana*, *Callistemon citrinus*, *Eucalyptus*

Figure 2. Botanical characteristics of camu camu and harvest strategies. Wild populations in flooding soils (A) and nonflooding soils (B), culture population in nonflooding soils (C), blooming flowers (D), unripe, semiripe, and ripe fruits (E), variations in seeds size (F), typical plant height and architecture (G), manual harvest during flooding period using canoes (H), and manual harvest in non-flooding soils.

grandis, *Gomidesia affinis*, etc.) [5]. Using flow cytometry, our research group recently determined that the genome size of camu camu is ~ 230 Mb (unpublished data), which is similar to *Myrciaria glazioviana* (234 Mb) [6] but is on the lower end of the range (234–1110 Mb) reported for Myrtaceae species [5].

2.5. Genetic diversity

Pioneering research analyzing the genetic diversity of camu camu was carried out with biochemical markers (esterases) by Brazilian researchers [7]. At that time, the presence of genetic structure was demonstrated among populations (two genetic groups) with an average heterozygosity of 0.08–0.14. Subsequent studies have analyzed the genetic diversity in germplasm collections and cultured populations using DNA markers, such as rapid amplification of polymorphic DNA (RAPD) [45], inter simple sequence repeat (ISSR) [8], expressed sequences tag-simple sequence repeats (EST-SSR) [9, 46, 47], and SSR [10, 11], also known as microsatellite markers. Overall, these investigations found that the average expected heterozygosity (*He* = 0.67 ± 0.19, range of 0.45–0.88) was greater than the average observed heterozygosity

Component per 100 g	Contents
Bromatological analysis	
Energy (kcal)	19.48 ± 3.68
Water	93.83 ± 0.51
Protein	0.51 ± 0.07
Carbohydrate	4.84 ± 0.80
Lipids	0.17 ± 0.10
Ash	0.22 ± 0.03
Crude fiber	0.56 ± 0.40
Total soluble solids (°Brix)	6.18 ± 0.99
pH	2.84 ± 0.31
Essential amino acids (mg/100 g)	
Valine	242.00 ± 104.65
Leucine	210.50 ± 111.02
Phenylalanine	32.50 ± 14.85
Threonine	32.00 ± 5.66
Essential fatty acids (% of total lipids)	
C18:3ω3 (α-Linolenic)	16.00 ± 0.70
C18:2ω6 (Linoleic)	9.70 ± 0.40
C18:3ω6 (γ-Linolenic)	9.30 ± 0.20
C20:5ω3 (EPA)	7.00 ± 0.10
Vitamins (mg/100 g)	
Vitamin C	2210.00 ± 650.00
Niacin	0.48 ± 0.28
Riboflavin	0.03 ± 0.02
Thiamine	0.01 ± 0.00
Minerals (mg/100 g)	
K	87.020 ± 29.382
PO_4	18.183 ± 8.122
SO_4	14.750 ± 2.192
Ca	14.510 ± 9.346
Cl	9.100 ± 3.536
Mg	7.393 ± 4.323
Co	1.173 ± 0.807
Na	0.934 ± 1.546
Mn	0.820 ± 1.118
Fe	0.424 ± 0.152

Component per 100 g	Contents
Al	0.255 ± 0.064
Zn	0.230 ± 0.138
Cu	0.117 ± 0.072
B	0.050 ± 0.000
Br	0.021 ± 0.005
Cr	0.015 ± 0.004
Mo	0.004 ± 0.002
Se (μg)	0.429 ± 0.089

Table 1. Nutritional composition of camu camu fruit pulp.

(*Ho* = 0.41 ± 0.06, range of 0.33–0.49). Also, the populations exhibited high inbreeding coefficients (*f* = 0.31 ± 0.13, range of 0.20–0.49) and high genetic differentiation values (F_{ST} = 0.26 ± 0.08, range of 0.21–0.32). Likewise, the average intrapopulation genetic diversity (average 74.89%, range of 65–79%) is ∼3 times greater than average interpopulation genetic diversity (average 25.10%, range of 20–35%). Also, these molecular markers studies demonstrated the presence of genetic structure among populations (from 2 to 3 genetic groups). However, two of these reports have shown that genetic and geographic distances are uncorrelated (*r* = 0.31, range of 0.23–0.39). These peculiar genetic population characteristics of camu camu can be partially explained as the result of their undomesticated condition and isolation of the populations by natural barriers, which limit gene flow and favor inbreeding. In conclusion, the genetic diversity characterization of camu camu in wild and artificial populations, and germplasm banks are still too fragmented and deficient to make any strong conclusions. Consequently, an in-depth knowledge of the genetic diversity of this species will be essential to implement programs for genome-wide genetic marker discovery and genotyping using next-generation sequencing technologies, which could then be used to quantify, with more precision and accuracy, the genetic diversity of camu camu across the entire Amazon region. Following this line of thought, our research group explored the assembled transcriptome of this species for molecular marker discovery. We identified more than 3200 SSR motifs that would be appropriate for developing a comprehensive set of genic-SSR markers. Also, the transcriptome contained a large number (>23,000) of high-quality single-nucleotide polymorphisms (SNPs) and marks the highest number of SNP markers discovered to date for camu camu using transcriptome sequencing [48]. Both types of potential molecular markers, however, will require validation.

3. Health-promoting phytochemicals

An ethnopharmacological survey of medicinal plants in the northeastern Amazon region of Peru showed that several botanical parts of camu camu such as immature and mature fruits, stems, leaves, roots, seeds, and barks are used to prepare remedies in folk medicine to treat numerous diseases such as arthritis, diabetes, hypercholesterolemia, bronchitis, inflammation,

asthma, atherosclerosis, cataracts, depression, flu, gingivitis, glaucoma, hepatitis, infertility, migraine, osteoporosis, Parkinson's disease, and malaria [49, 50]. Additionally, Steele [51] showed that camu camu is used traditionally for the treatment of malaria by indigenous people of South America. All these traditional uses are in concordance with multiple scientific researches showing that several botanical parts of camu camu are a rich source of various health-promoting phytochemicals with proved health beneficial properties. Among these bioactive phytochemicals, in addition to vitamin C, several secondary metabolites exist such as polyphenols, carotenoids, and other chemicals, which are presented in **Figures 3** and **4** and detailed below.

3.1. Antioxidative and antiinflammatory activities

A large amount of scientific information currently exists regarding the antioxidant properties of camu camu fruits that were collected by diverse methods, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH assay), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), ferric reducing ability of plasma (FRAP assay), oxygen radical absorbance capacity assay (ORAC assay), total radical-trapping antioxidant parameter (TRAP assay), β-carotene bleaching method, cupric ion reducing antioxidant capacity (CUPRAC assay), total oxidant scavenging capacity (TOSC assay), Trolox equivalent antioxidant capacity (TEAC assay), peroxyl radical scavenging capacity (PSC assay), and pulse voltammetry measurements (voltammetric electronic tongues) [16, 17, 21, 52–54]. Pioneering work on antioxidant properties of camu camu was realized by Reynertson et al. [25], who obtained a IC_{50} value of 57.2 μg/mL on the dried, powdered fruit with the DPPH assay. This low value indicates large antiradical activity, and compared with other Myrtaceae fruits, it was considered very active. These properties were attributed to the high content of vitamin C and total phenolic phytochemicals (101 ± 0.25 mg gallic acid equivalent/g dry weight). Furthermore, Sotero et al. [55] reported that a methanolic extract of fruit pulp, fruit peel, and seeds have antioxidant activities with IC_{50} values of 167.7, 146.9, and 399.8 μg/mL, respectively, with the DPPH assay. Also, De Souza Schmidt Gonçalves et al. [56] demonstrated that lyophilized pulp presented the highest antioxidant capacity with the DPPH assay (∼1450 μmol trolox equivalent/g dry weight) and ORAC assay (∼800 μmol trolox equivalent/g dry weight), which was ≥10 times higher than 21 other native Brazilian fruits analyzed. Positive correlations were high and significant (r = 0.989 [DPPH vs. total phenolics content], and r = 0.795 [ORAC vs. total phenolics content]) between the antioxidant capacity and total phenolics content (∼285 mg catechin equivalent/g dry weight). Additionally, in the fresh fruit pulp, Sánchez [57] found antioxidant capacity values of 219.7 μmol trolox equivalent/g fresh weight and 214.1 μmol trolox equivalent/g fresh weight with the DPPH and ABTS assays, respectively. Another study conducted by Villanueva-Tiburcio et al. [52] compared the antioxidant activity in fruit peel of three maturation stages (unripe, semiripe, and ripe). Semiripe fruits showed the highest antiradical power with the DPPH (IC_{50} = 46.20 μg/mL), ABTS (IC_{50} = 20.25 μg/mL), and PSC (IC_{50} = 8.30 μg/mL) assays. Again, the authors corroborated a highly positive correlation of vitamin C and polyphenol content with the ability to inhibit the free radical DPPH (r = 0.999 with both compounds). Several other investigations have corroborated the highly positive correlations between polyphenol content and antioxidant activity with different assays. Likewise, the superior antioxidant capacity of camu camu fruits was established by the comparison

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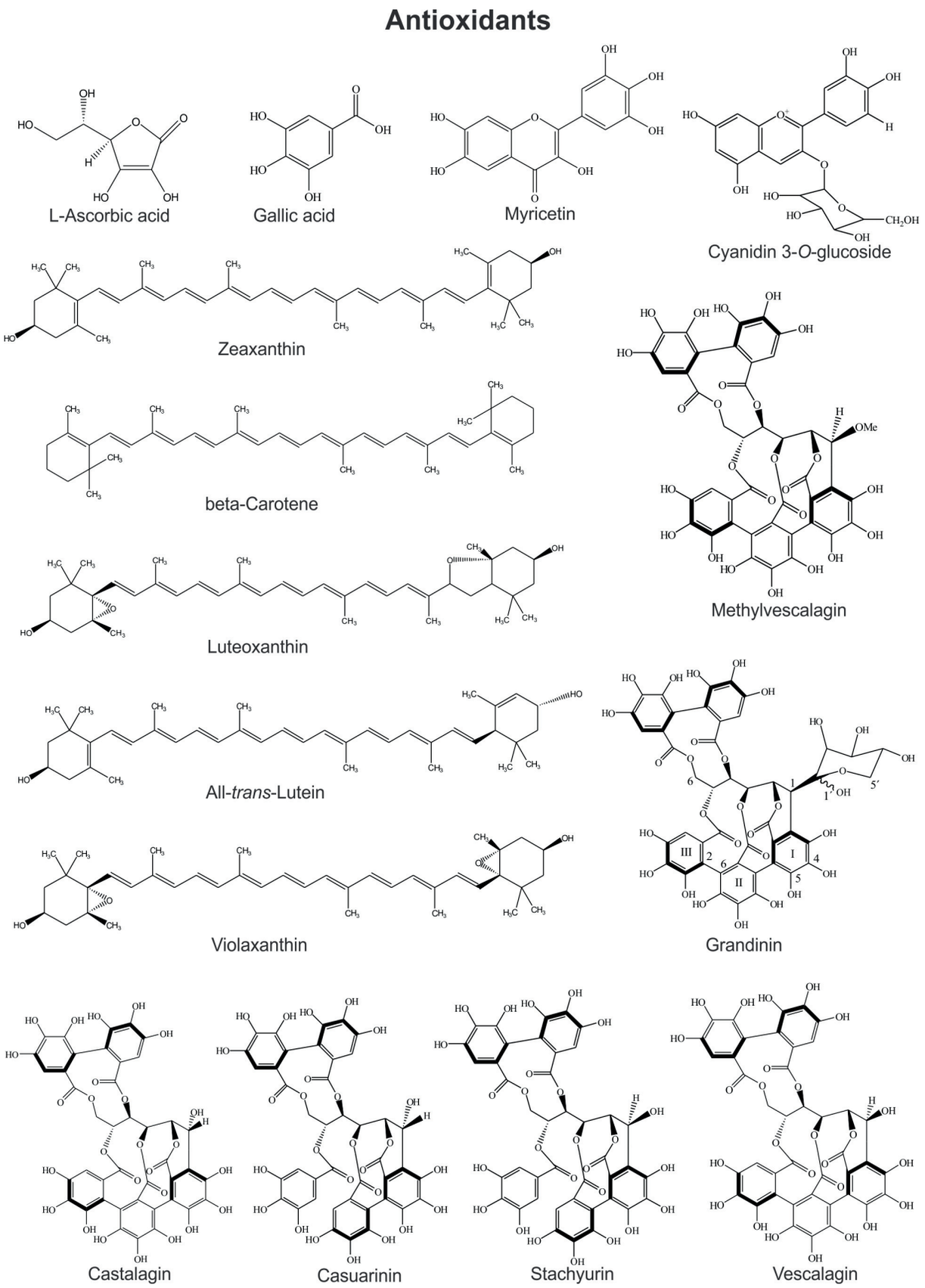

Figure 3. Some phytochemical compounds with antioxidant activities identified in fruits of camu camu.

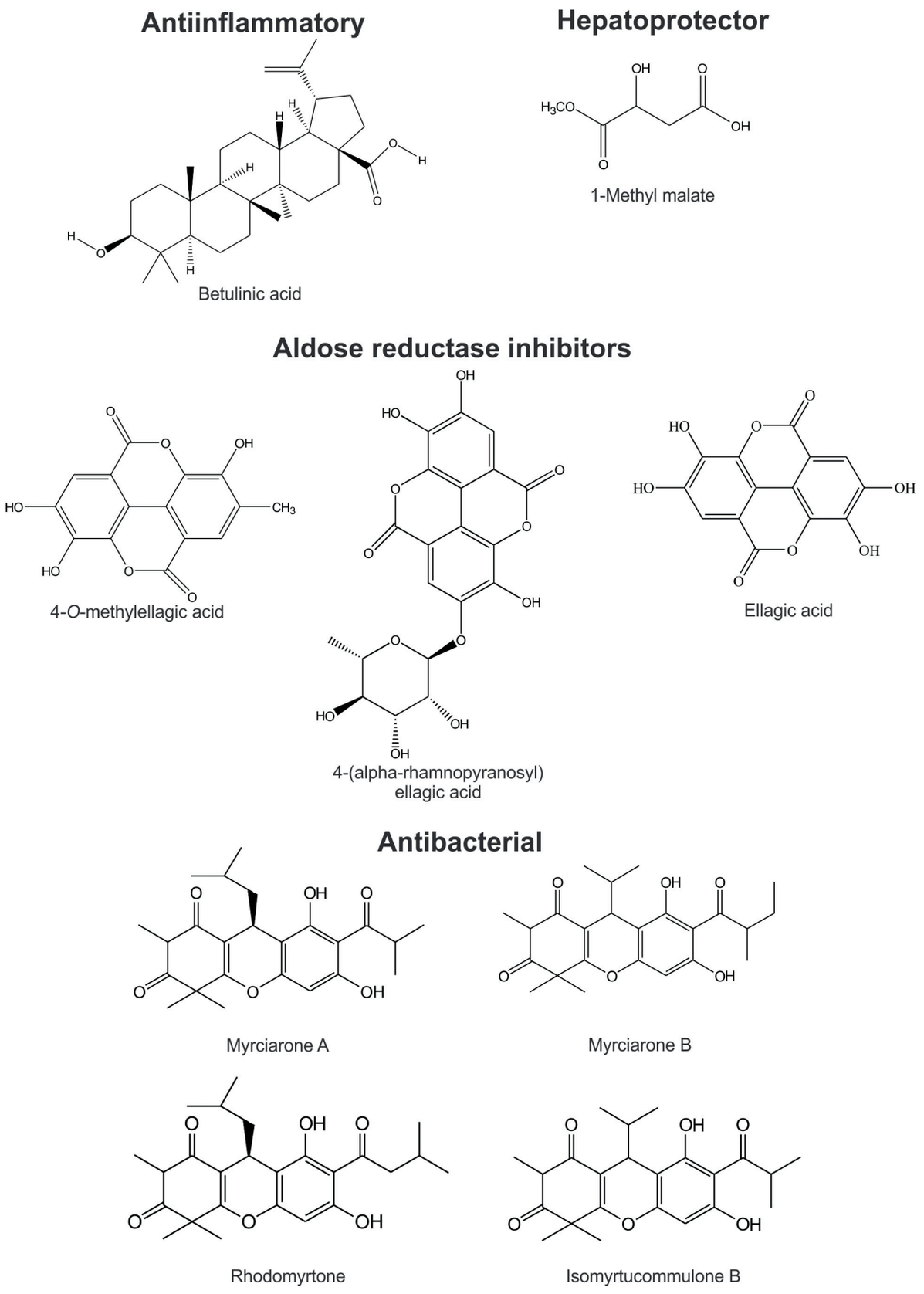

Figure 4. Phytochemical compounds with corroborated health-promoting phytochemicals isolated by bioassay-guided approaches from camu camu tissues.

of other plant species [16, 17, 19, 58–60]. An in-depth analysis of phenolics compounds was realized by Fracassetti et al. [17]. These researchers identified 53 different phenolics (flavonols [6], anthocyanins [1], ellagic acid and derivatives [10], ellagitannins [10], gallic acid and derivatives [2], and proanthocyanidins [24]) and found differential quantities of these compounds in fruit pulp, peel, seeds, and two powder products from camu camu fruits. Interestingly, the flour produced from the remaining peel, seeds, and adhered pulp after pulp extraction showed a superior vitamin C and phenolics content than the pulp powder (2.6 and 13.9 times, respectively). In addition, the flour displayed greater antioxidant capacity than the pulp power (from 2.0 to 4.5 fold).

In vivo studies using *Rattus norvegicus* (Wistar strain) as an experimental model that were treated orally with fruit pulp and tropical juice containing 5% of camu camu fruit pulp demonstrated a significant increase in plasma antioxidant capacity, liver glutathione peroxidase, superoxide dismutase, and catalase activities and thiobarbituric acid-reactive substances were reduced when compared with control [61, 62]. Finally, Inoue et al. [22] analyzed the antioxidant and antiinflamatory activities of camu camu juice in 10 healthy habitual smokers. The participants ingested 70 mL of juice (100% fruit pulp) daily for 7 days. After the experimental period, the oxidative stress markers such as levels of urinary 8-hydroxy-deoxyguanosine and total reactive oxygen species decreased significantly ($p < 0.01$) in the camu camu group. Similar trends were evident with inflammatory markers such as serum levels of high-sensitivity C reactive protein, interleukin 6, and interleukin 8, while the group that ingested vitamin C tablets remained unchanged. The researchers concluded that the fruit juice of camu camu may have powerful antioxidant and antiinflammatory properties compared to vitamin C tablets, due to the existence of unknown antioxidant substances modulating *in vivo* vitamin C in camu camu. These health-promoting activities can be partially explained based on current evidence that the ingestion of the fruit pulp and other derived products significantly increase the postprandial antioxidant capacity of the plasma [63] due to the high vitamin C and polyphenolics content.

Additionally, in previous animal experiments using *Mus musculus* as carrageenan-induced paw edema model, a Japanese research group demonstrated that the methanolic extract of seeds significantly reduced edema formation with regard to size and volume in a dose-dependent manner. These antiinflammatory effects were associated with inhibition of the localized nitric oxide production by macrophages. Further, by bioassay-guided fractionation, the researchers identified the active compound to be 3β-hydroxy-lup-20(29)-en-28-oic acid (betulinic acid) [23].

3.2. Antiobesity, hypolipidemic, and antihypertensive activities

Several studies in animal models and humans have corroborated the beneficial effects of camu camu fruits on the improvement of biochemical lipid profiles. For example, in animal experiments conducted by Schwertz et al. [24], Wistar rats (*R. norvegicus*) were induced to a dyslipidemic condition by a high-fat diet and then were subjected to various treatments with camu camu fruit juice (0.4–10 mL/kg) for 2 weeks. All dosages showed an improvement in the biochemical lipid profile in a dose-dependent manner, which was evident by a significant reduction in triacylglycerols, total cholesterol, and hepatic cholesterol. Further, fecal cholesterol

excretion was increased. In addition, assays performed by Nascimento et al. [44] in a rat model of diet-induced obesity that ingested daily 25 mL of camu camu fruit pulp by 12 weeks resulted in a significant weights reduction of the fat in white adipose tissues. Triacylglycerols (↓40.6%), total cholesterol (↓39.6%), LDL cholesterol (↓2.14%), and VLDL cholesterol (↓36.4%) levels were also decreased, and HDL cholesterol (↑12.3%) increased in experimental groups. Similar experiments conducted by De Souza Schmidt Gonçalves et al. [61] in a type 1 diabetic rat model (streptozotocin induced) receiving oral administration of 1 or 3 g/kg by body weight of aqueous fruit pulp extract by 30 days, significantly reduced triacylglycerols and total cholesterol levels, and an increase in HDL cholesterol. Additionally, some controlled clinical trials with healthy young adults (20–35 years old) who received oral administration of pulp nectar [64] or encapsulated freeze-dried pulp for approximately 2 weeks [65, 66] displayed a significant improvement in their biochemical lipid profiles, due to hypolipidemic effects. The improvement in the biochemical profile of obesity is associated with an increase in lipid elimination in feces (50%) and by the liver (140%) due to the existence of dietary fiber in the fruit pulp [2, 41]. Dietary fibers have shown multiple beneficial health properties by their role in energy intake regulation and obesity development, which are related to its peculiar physicochemical characteristics. Some mechanisms suggested how dietary fiber aids in weight management include promoting satiation, extended signals of satiety, decreasing transport of macronutrients, and altering secretion of gastrointestinal hormones [67–71].

An *in vitro* study based in the angiotensin converting enzyme-1 (ACE) inhibition displayed that the camu camu fruit pulp lacks antihypertension properties in the 10-mg/mL aqueous extract [26]. However, when spray-dried powders of fruit pulp were added (0.5–1.0%) to samples of lactic acid bacterial fermented soymilk, there was a higher ACE inhibitory effect, suggesting a synergic interaction between camu camu and soymilk active compounds.

3.3. Antidiabetic activity

Some studies have shown that camu camu has antidiabetic activities, which may indicate its potential to treat this disease. For example, studies conducted by De Souza Schmidt Gonçalves et al. [56], De Azevêdo et al. [59], and Fujita et al. [26, 72] with fruit methanolic and polyamide-purified extracts, fruit depulping residue, pulp extract powders (spray drying and freeze-drying), and a probiotic beverage from dried powder of fruit pulp combined with soymilk, respectively, have shown *in vitro* antidiabetic properties due to the combination of moderate alpha-amylase and potent alpha-glucosidase inhibitory activities. This antienzymatic association is considered appropriate as means of modulating carbohydrate digestion and retarding postprandial glycemia, which is an efficient strategy to manage early stages of diabetes type 2 [73]. Also, an *in vivo* assay with obese male *R. norvegicus* conducted by Nascimento et al. [44] treated with 25 mL of pulp for a duration of 4 weeks showed a significant reduction in both blood glucose (23%) and insulin activities (44.5%). The authors attribute the hypoglycemic activity to the large quantity of soluble fibers (**Table 1**) that form complexes with monosaccharides. Furthermore, studies with healthy young adults (20–35 years old) who received oral administration of pulp nectar [64] or encapsulated freeze-dried pulp displayed a significant hypoglycemic effects in 15 days [65, 66]. Finally, Balisteiro et al. [63] showed that healthy subjects that have ingested a polyphenols-rich juice of camu camu significantly reduced the blood glucose levels

(31%) after a carbohydrate-rich meal ingestion. The hypoglycemic activity of these preparations can be attributed to polyphenols of the camu camu fruits. Polyphenols have two corroborated hypoglycemic mechanisms. The first is related to inhibitory action of the carbohydrate digestive enzymes alpha-amylase and alpha-glucosidase [26, 44, 56, 63, 72] because these inhibitory activities have high-positive correlations (Pearson's correlation coefficient ≥ 0.50) with the concentration of different phenolic compounds (casuarictin, ellagic acid, quercetin, syringic acid, myricetin, etc.) [26, 56]. Second, intestinal monosaccharides transporters such as sodium-dependent glucose transporter 1 (SGLT1) and glucose transporter 2 (GLUT2) were inhibited, which was demonstrated in several studies [74–79].

Additionally, Ueda et al. [80] isolated three aldose reductase (AR) inhibitors from an 80% methanolic leaf extract: ellagic acid, 4-*O*-methylellagic acid, and 4-(α-rhamnopyranosyl)ellagic acid. The last phenolic compound showed the strongest uncompetitive inhibition against human recombinant AR and rat lens AR. Also, the inhibitory activity of 4-(α-rhamnopyranosyl)ellagic acid was 60 times more powerful than quercetin. Consequently, these AR inhibitors are able to prevent the biochemical conversion of glucose to sorbitol in the polyol pathway and then reduce diabetic complications [81–83].

3.4. DNA damage and cancer protection effects

Mus musculus (CF-1™ strain) were used by Da Silva et al. [27] to test the genotoxic and antigenotoxic potential of camu camu fruit juice after acute (single dose for one day), subacute (for 28 consecutive days), and chronic (for 56 consecutive days) oral administration. None of the fruit juice concentrations (25, 50, and 100%) tested exerted any genotoxic effect on blood cells in male and female mice. In the *ex vivo* test, with the alkaline comet assay, the fruit juice demonstrated antigenotoxic effect after acute, subacute, and chronic treatments. However, the acute administration of the fruit juice produced the lowest values in both damage index and damage frequency. The researchers associated the protective effect, against DNA damage caused by hydrogen peroxide, to the elevated levels of vitamin C, as well as to the flavonoids and phenolic compounds present in the fruit juice of camu camu; together these phytochemicals are very able to eliminate free radicals.

Furthermore, several studies using microbial and animal models have demonstrated the antimutagenic properties of the camu camu fruits. In Peru, pioneering investigations were conducted by Gutiérrez [28], who tested the antimutagenic properties of an aqueous extract of fruit using *in vitro* and *in vivo* models. In the *in vitro* model, cultures of the CHO-K1 cell line from hamster (*Cricetulus griseus*) ovary were exposed to hydrogen peroxide and co-treated with fruit extract (concentrations at 1, 5, and 10%). The camu camu fruit extract had a significant capacity to protect against chromosomal aberrations induced by reactive oxygen species in a dose-dependent manner. Also, in the *in vivo* model using fruit fly (*Drosophila melanogaster*) specimens, the antimutagenic activity of the fruit extract against the mutagenic effect induced by N-ethyl-N-nitrosourea (concentrations at 0.01 and 0.1 mmol) was demonstrated. This DNA damage protection effect was tested by the somatic mutation and recombination test that displayed a significant reduction in the frequency of wing spots (55.0–74.4%) in flies co-treated with 25% of fruit aqueous extract. In addition, Sánchez [57] demonstrated with the Ames test that a phenolic compound-rich fraction from the fruit pulp displayed antimutagenic activity (36.7–91.5%) in a

dose-dependent manner against the mutagenic compound 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole. Further, in the two investigations on the frequency of micronucleated polychromated erythrocytes of bone marrow cells of albine mice (*M. musculus*) induced with cyclophosphamide and co-treated with fruit pulp by orogastric gavage for 10–15 consecutive days, there was a significant and drastic (from 16 to 90%) reduction of micronucleous frequency in a dose-dependent manner [21, 84]. Additionally, the cytoprotective activity of the camu camu fruit against the mutagenic damage caused by potassium bromate ($KBrO_3$) was also demonstrated. Animals were treated by oral administration of a fruit aqueous extract (50 mg/kg) for 35 consecutive days. In the tenth day of treatment, albine mice were intraperitoneally injected with a solution of $KBrO_3$ (dosage of 68.5 mg/kg) to induce mutagenic injury. After a meticulous comparative analysis of the DNA fragmentation degree, with the alkaline comet assay, a great inhibitory capability of the fruit pulp against the DNA-damaging effects of $KBrO_3$ in blood, kidney, and liver cells was noticeable. This strong protective action was potentially attributed to the high content of antioxidants such as vitamin C and flavonoids present in the fruits of this fabulous Amazonian plant [85].

Recent reports also demonstrated the anticancer properties of camu camu fruit juice. In the first research conducted by Carvalho-Silva et al. [21], the authors used an *in vitro* cytotoxicity and antiproliferative assays. In these tests, the HepG2, a liver hepatocellular carcinoma cell line, was grown for 72 hours in media containing increasing concentrations (0–25 mg/mL) of a tropical fruit juice mix that contained fruit pulp of camu camu at 5%. The results indicate that the tropical fruit juice mix provided anticancer activity against HepG2 cell line because the proliferation ratio was inhibited in a dose-dependent manner (from 10 to 80%, approximately). Also, there was no cytotoxic effect up to 150 mg/mL, suggesting that the anticancer effect was independent of cytotoxicity. These health-promoting actions were associated with the high levels of vitamin C and anthocyanins (i.e., cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, cyanidin-3-*O*-rhamnoside, etc.) present in the tropical plant beverages that together contribute to the great antioxidant capability, consequently decreasing the free radicals to the lowest level and then the risk of cancer. The second study conducted by Asmat and Benites [86] used an *in vivo* experimental model. In this study, one group of *R. norvegicus* (Albinus strain) was injected subcutaneously with 21 mg/kg of 1,2-dimethylhydrazine from week 2 to 22 to induce colorectal cancer and co-treated from week 1 to 32 with fruit extract (containing fruit pulp and peel) at a dosage of 4.37 g/kg. The control group also received treatment to develop colorectal cancer but received a standard diet and water *ad libitum* for 32 weeks. The fruit extract of camu camu interfered with the progression to histological alterations such as metaplasia. In contrast, the control group showed major structural damage, pseudostratification, necrosis, and high mitotic index. Once again, this demonstrated the multiple beneficial properties of camu camu fruits.

3.5. Hepatoprotective activity

Akachi et al. [18] conducted experiments with *R. norvegicus* (Wistar strain), which were fed for 7 days with lyophilized fruit juice of camu camu or one of 11 other fruit juices (*Averrhoa carambola*, *Citrus depressa*, *Hippophae rhamnoides*, *Hylocereus costaricensis*, *Litchi chinensis*,

Malpighia glabra, *Passiflora edulis*, *Punica granatum*, *Ribes nigrum*, *Vaccinium corymbosum,* and *V. oxycoccus*). The liver of the rats was then injured by the injection of D-galactosamine (GalN). Only the juice of camu camu significantly suppressed the GalN-induced liver injury. This hepatoprotective activity was due to the active compound 1-methylmalate, which was isolated by bioassay-guided solvent fractionation and silica gel column chromatography of the camu camu fruit juice. To date, however, the molecular mechanism by which this active compound suppresses GalN-induced liver injury remains undiscovered. Similarly, the specific metabolic pathway and enzymes involved in the biosynthesis of 1-methymalate in camu camu are unknown. It is probable that the Krebs cycle provides malate for the biosynthesis of this active compound, and specific S-adenosyl-L-methionine-dependent methylation of carboxyl groups methyl transferase adds the methyl moiety in carbon 1 of malate, which remains undiscovered.

3.6. Neuroprotective and immunological effects

The effect of hot air-dried residue of camu camu fruits (seeds, peel, and residual pulp) on the neuroprotective effects in experimentally induced neurodegeneration was evaluated in *Caenorhabditis elegans* transgenic models for Alzheimer's disease and Parkinson's disease [87]. Treatments with low molecular weight fraction of hot air-dried residue significantly extended the life span in *C. elegans* by 20% and delayed $A\beta_{1-42}$ aggregation induced paralysis by 21% in the Alzheimer's disease model. Additionally, in the 1-methyl-4-phenylpyridinium-induced oxidative dopaminergic neurotoxicity model for Parkinson's disease treatment with the same fraction of the fruit extract resulted in significant abrogation in neurotoxicity by 15–21%. These health-relevant effects were inferred mostly due to polar acidic low-molecular-weight bioactive fractions.

Recently, a Brazilian research group [88] evaluated the effect of the oral administration of the fruit powdered pulp extract in immunological parameters in *Oreochromis niloticus* (Nile tilapia). Fishes were fed for 5 weeks using various dosages (0–500 mg of camu camu extract/kg of feed). At the end of the trial period, fishes were inoculated in the swim bladder with the pathogenic bacteria *Aeromonas hydrophila* to induce an acute aerocystitis. The immunological parameters were then analyzed after 6, 24, and 48 h of the infection. Results revealed that fish supplemented with camu camu fruit extracts had significantly increased immunological responses by increasing the white blood cells counts and exudate (lymphocytes, monocytes, neutrophils, and thrombocytes), leukocyte respiratory burst, serum lysozyme activity, serum bactericidal activity, direct agglutination, and melanomacrophage centers count. Notably, an increase in fish growth after 5 weeks, especially, at a dose of 500 mg/kg was detected.

Also in pre-clinical studies using *R. norvegicus* (Holtzmann strain) with oral administration of an aqueous extract of fruit pulp (5 and 10%) by 5 days, the authors displayed a greater immunostimulatory activity in a dose-dependent manner, after the treatments with the vegetable beverage [89]. This immune stimulant action was in two ways, first was by increasing the number of circulating mature lymphocytes (~2 times) and the second mechanism was by stimulating the phagocytic activity of the reticulum endothelial system (in average 75.71%).

3.7. Antibacterial and antiparasitic activities

Recently, several research groups have investigated the antibacterial and antiparasitic activities of botanical extracts from camu camu. With respect to antibacterial activity, the first report was from a Japanese research group (Myoda et al. [19]) who showed that the methanolic extracts (100% methanol) from fruit peel and seeds have strong antimicrobial activity against *Staphylococcus aureus* at 5 mg/mL, suggesting that lipophylic chemicals are responsible for the selective antistaphylococcal activity. Also, a Peruvian research group reported the antistaphylococcal activity of hydroalcoholic extracts (70% ethanol) derived from leaves and bark [90]. Again, Brazilian researchers recorded antistaphylococcal activity of the lyophilized pulp, spouted bed dried pulp, and spray-dried pulp with minimum inhibitory concentration (MIC) of extracts of 0.08 mg/mL [26, 91]. Similarly, another Brazilian research group showed the antistaphylococcal activity of the fruit industrial residue (seeds and peel). Both fresh, freeze dried, and hot air dried residues showed higher inhibition zones (>10 mm) and lower MIC (0.31–2.50 mg/mL) against *S. aureus*. In addition, the polyphenolic-rich fractions provided these antibacterial activities with inhibition zones from 13.1 to 16.1 mm and MIC value of 2.5 mg/mL. Furthermore, another Peruvian research group demonstrated that methanolic extracts from pulp and seeds possess higher antibacterial effects against the cariogenic bacteria *Streptococcus mutans* and *S. sanguinis*. The MIC of the pulp extract showed a range of 50–75 μg/mL; however, the seed antibacterial activity was detected at very low levels [92]. Finally, recently another Japanese research group isolated four polyphenolic antimicrobial constituents (acylphloroglucinols) from the n-hexane extracts of peel and seeds, these compounds were Isomyrtucommulone B, Myrciarone A, Myrciarone B, and Rhodomyrtone. The second and third compounds were confirmed to be new acylphloroglucinols [20]. The four compounds showed antimicrobial activities against Gram-positive bacteria such as *Bacillus subtilis*, *B. cereus*, *Micrococcus luteus*, *S. aureus*, *S. epidermidis*, and *S. mutans* but were inactive against Gram-negative bacteria and fungi. Several investigations at transcriptomic, proteomic, and metabolomic levels have revealed the molecular mechanism involved in the antimicrobial activity of Rhodomyrtone against Gram-positive bacteria [93–96].With respect to antiparasitic activities, researchers from England [51, 97] reported that a mixture of 10 myricetin and quercetin glycosides isolated from the aqueous acetic acid–soluble fraction of methanolic extracts of camu camu were potent inhibitors of the GSH-haemin reaction. Also, the aqueous ethanolic extract (70%) of fruit peel, leaves, and seeds exhibited antiplasmodial activity with the ferriprotoporphyrin inhibition test with IC_{50} < 5.0 μg/mL [50]. Additionally, the aqueous and the ethanolic (70%) extracts from the bark displayed inhibitory activity against the *Plasmodium falciparum* strain FCR3 (chloroquine resistant) with IC_{50} values of 3 and 6 μg/mL, respectively [98]. In addition, the dichloromethanolic extract of camu camu leaves exhibited a significant in vitro growth inhibition of *P. falciparum* and *Leishmania amazonensis* with IC_{50} values of 1.05 and 6.41 μg/mL, respectively [99].

3.8. Other bioactivities

Animal experiments using *R. norvegicus* to test the effect of a fruit extract of camu camu alone and in combination with a powdered tuber extract of black maca (*Lepidium meyenii*) showed

that camu camu fruits extract significantly increased the daily sperm production, stages IX and XI of mitosis and stage XII of meiosis. In combination with black maca, spermiation stages, mitosis, and meiosis were increased. The authors concluded that camu camu fruits potentially improve spermatogenesis and mixing with black maca tubers increased the stages of mitosis, meiosis, and spermiation of the spermatogenic cycle as assayed by the transillumination technique [100].

Additionally, two *in vitro* investigations demonstrated that the hydroalcoholic and aqueous fruit extracts (containing peel, pulp, and seeds) of camu camu could be added in cosmetic formulations, since fruit extracts empower the sun protection factor against UVB radiation. This peculiar characteristic is attributable to the high levels of vitamin C and phenolic compounds in the fruit [101, 102].

Finally, a research of Yuyama et al. [103] demonstrated the beneficial impacts of mixing fruits pulp of camu camu and *Euterpe oleracea* to treat preschool children (2–6 years old) with anemia and chronic malnutrition.

4. Functional genomic characteristics

4.1. Transcriptome *de novo* asembly and annotation

Recently, our research group used a total of 24,551,882 high-quality reads to assemble the fruit (unripe, semiripe, and ripe) transcriptome of camu camu. In total 70,048 unigenes were obtained in the meta-assembly (mean length of 1150 bp and N_{50} = 1775 bp). These unigenes were annotated by searching homologous sequences in multiple databases (i.e., NCBI nonredundant (nr), UniProtKB, TAIR, GR_protein, FB, MGI, etc.). The top three plant species that contributed the greatest number of gene annotations were *Vitis vinifera*, *Theobroma cacao*, and *Populus trichocarpa*. Of the three core GO annotation categories, biological processes comprised 53.6% of the total assigned annotations, whereas cellular components and molecular functions comprised 23.3 and 23.1%, respectively. In total, 160 metabolic pathways were reconstructed [48].

4.2. Metabolic pathways for vitamin C biosynthesis

Based on the fruit transcriptome analysis, five metabolic pathways for vitamin C biosynthesis [48] were reconstructed: animal-like pathway, myo-inositol pathway, L-gulose pathway, D-mannose/L-galactose pathway, and uronic acid pathway. Gene coding enzymes involved in the ascorbate-glutathione cycle were also identified (**Figure 5**). From these pathways, the D-mannose/L-galactose pathway is the best characterized in several plant species [104–106]. This pathway involves the sequential enzymatic conversion of D-mannose-1-phosphate in to Vitamin C. These enzymatic reactions are as follows: GDP-D-mannose synthesis from D-mannose-1-phosphate and GTP is catalyzed by GDP-D-mannose pyrophosphorylase (E.C. 2.7.7.13), and then, GDP-D-mannose is converted to GDP-L-galactose by a reversible double epimerization, catalyzed by GDP-mannose-3′,5′-epimerase (E.C. 5.1.3.18); further, GDP-L-galactose is

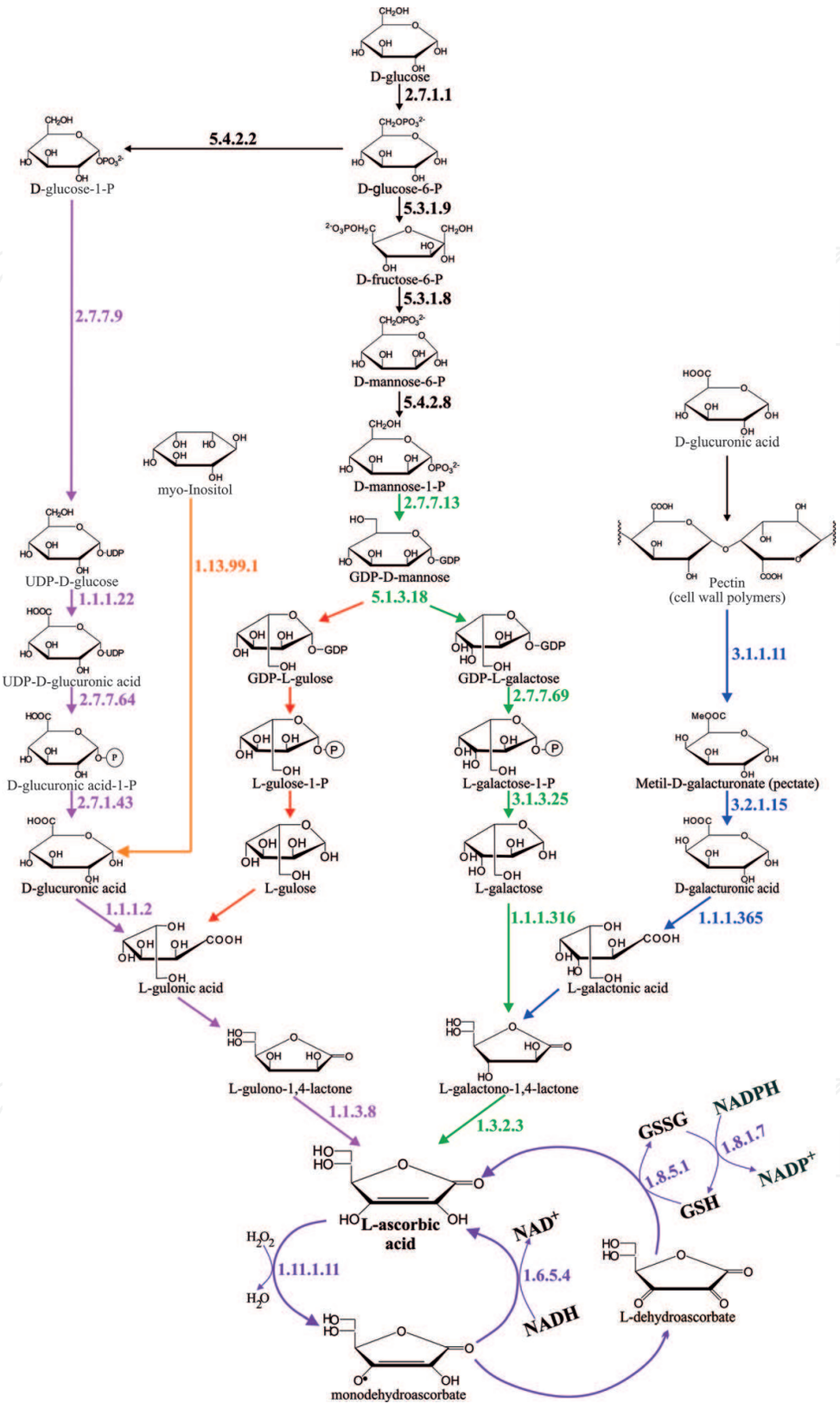

Figure 5. Vitamin C biosynthesis and recycling pathways reconstructed from the fruit transcriptome database of camu camu. Source: Castro et al. [48].

transformed by GDP-L-galactose:hexose-1-phosphate guanyltransferase (E.C. 2.7.7.69) to L-galactose-1-phosphate, which is subsequently hydrolyzed to L-galactose and inorganic phosphate by L-galactose-1-phosphate phosphatase (E.C. 3.1.3.25). L-galactose is next oxidized to L-galactono-1,4-lactone by the NAD-dependent L-galactose dehydrogenase (E.C. 1.1.1.316), and finally, L-galactono-1,4-lactone is oxidized to vitamin C by L-galactono-1,4-lactone dehydrogenase (E.C. 1.3.2.3).

4.3. Metabolic pathways involved in health-promoting phytochemicals biosynthesis

As previously mentioned, most of the health-promoting phytochemical compounds identified in camu camu are specialized metabolites, commonly known as secondary metabolites. Biosynthesis of these structural diverse molecules starts from key basic pathways, for instance the Embden-Meyerhof-Parnas pathway (also known as the glycolysis), pentose phosphate pathway, and the Shikimate pathway. The latter pathway produces chorismate, a common precursor for the tryptophan pathway, the phenylalanine/tyrosine pathways, and the metabolic pathways for the biosynthesis of folate, salicylate, and phylloquinone [107]. Subsequently, these three aromatic amino acids are used as biosynthetic precursors in several metabolic pathways to produce a diverse array of secondary metabolites (i.e., terpenoids, phenolic compounds such as flavonols, anthocyanins, ellagic acid and derivatives, ellagitannins, gallic acid and derivatives, etc.), depending on several biological and environmental factors [108]. From the annotated fruit transcriptome of camu camu, we were able to reconstruct more than 160 metabolic pathways [48]. These include several pathways involved directly in secondary metabolite biosynthesis, for example, the anthocyanins, carotenoids, flavonoids, phenylpropanoids, and terpenoids biosynthesis pathways. The universal biosynthetic precursor (chorismate) for all these pathways is synthesized in the Shikimate pathway (**Figure 6**). In this pathway, seven enzymatic reactions biochemically transform phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate (metabolic intermediates in glycolysis and the pentose phosphate pathways, respectively) to chorismate. The first committed step of the shikimate pathway is an aldol condensation of phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate to produce 3-Deoxy-D-arabino-heptulosonate-7-phosphate (DAHP), this reaction is catalyzed by DAHP synthase (E.C. 2.5.1.54). Further, 3-Dehydroquinate synthase (E.C. 4.2.3.4) converts DAHP to 3-dehydroquinate using a divalent cation (i.e., Co^{2+}) and NAD+ cofactors via five consecutive chemical reactions: alcohol oxidation, β-elimination of inorganic phosphate, carbonyl reduction, ring opening, and intramolecular aldol condensation. The third enzymatic reaction catalyzed by 3-dehydroquinate dehydratase (E.C. 4.2.1.10) includes the dehydration of 3-dehydroquinate to 3-dehydroshikimate to introduce the first double bond in the ring, and the fourth reaction catalyzed by shikimate:$NADP^+$ oxidoreductase (E.C. 1.1.1.25) is a reversible reduction of 3-dehydroshikimate into shikimate using NADPH. The fifth enzyme (shikimate kinase [2.7.1.71]) catalyzes the phosphorylation of the C3 hydroxyl group of shikimate using ATP as inorganic phosphate donor to yield shikimate-3-phosphate. Then, 5-enolpyruvyl-shikimate-3-phosphate (EPSP) synthase (E.C. 2.5.1.19) catalyzes the formation of EPSP, by transferring the enolpyruvyl moiety of PEP to the 5-hydroxyl position of shikimate-3 phosphate. Finally, chorismate synthase (E.C. E.C. 4.2.3.5), the last enzyme of the shikimate

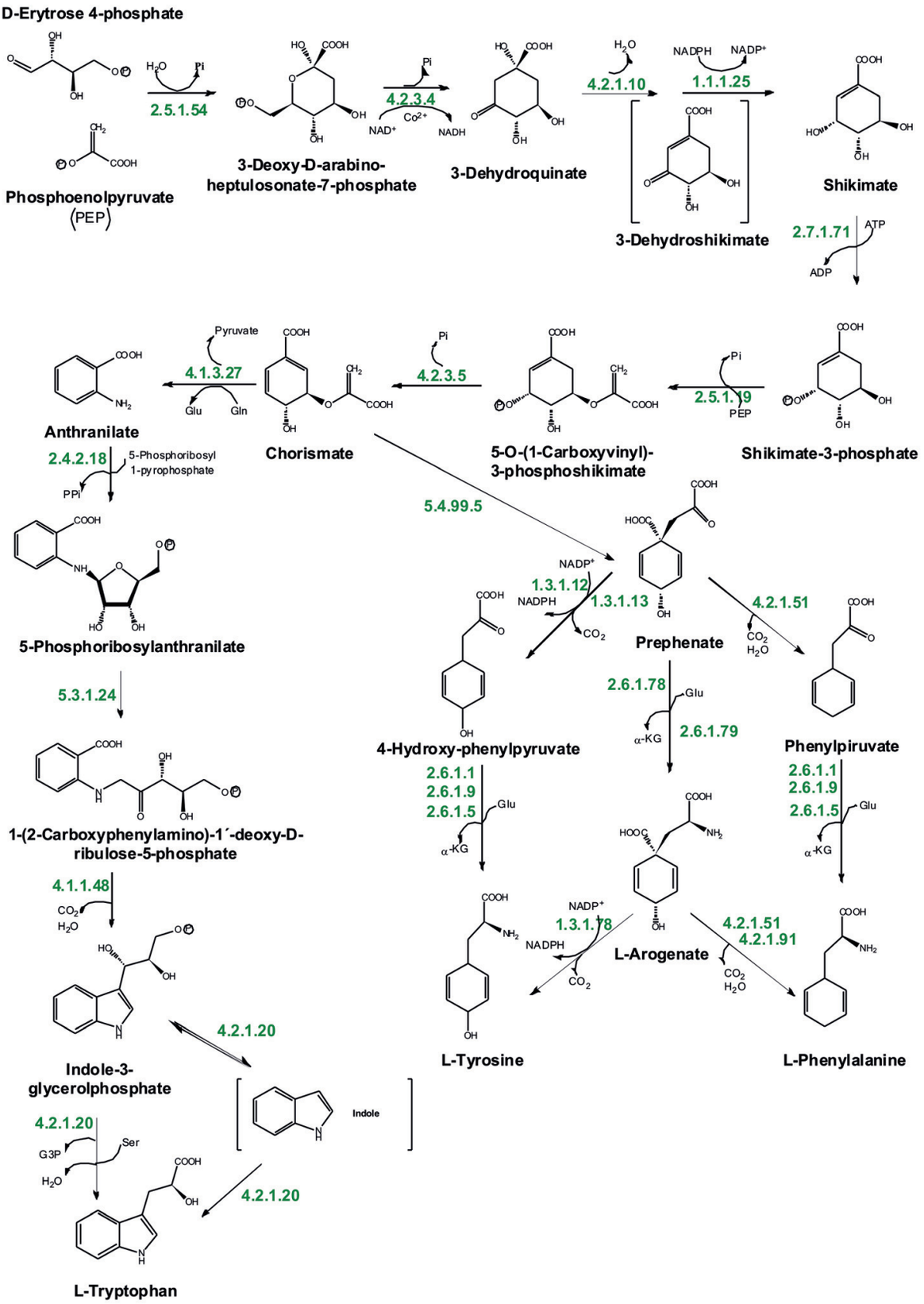

Figure 6. The Shikimate pathway reconstructed from the fruit transcriptome database of camu camu.

pathway, is itself biochemically unique in nature and catalyzes a 1,4-antielimination of the 3-phosphate group and C6-pro-R hydrogen from EPSP, introduces the second double bond in the ring to produce chorismate [107].

5. Domestication strategy and efforts for genetic improvement

Some Peruvian research Institutions such as the National Institute of Agricultural Innovation (INIA), the Research Institute from the Peruvian Amazon (IIAP), and the Veterinary Institute for Tropical and High Altitude Research (IVITA), as well as Brazilian research Institutions such as the National Institute of Amazonian Research (INPA) and the Brazilian Agricultural Research Corporation (EMBRAPA), have implemented programs for *ex situ* conservation of camu camu. These genetic conservation programs involve the establishment of germplasm banks composed by accessions of botanical material collected from wild populations. In Peru, germplasm banks were established about 37 years ago [109] from seeds (due to the lack of vegetative propagation techniques) obtained from only 40% of the wild populations in the Loreto region (Imán S., personal communication, September 15, 2017). Consequently, further prospecting and collecting of botanical samples need to be carried at regional and distribution wide levels to maximize greatest genetic diversity. The efficiency of increasing banked accessions could be improved by incorporating vegetative propagation techniques. The two most plausible alternatives are improved grafting and root cuttings techniques, developed and refined by Peruvian and Brazilian researchers [110–112].

The domestication process of camu camu was promoted by INIA and IVITA at the beginning of the 1990s with the installation of seven demonstration parcels in the community of Santa Ana, which are located in the Amazon River ~30 km from Iquitos [109]. Further, since the beginning of the twenty-first century, INIA in association with IIAP implemented a genetic improvement program using an active community participation strategy and conventional plant breeding methods, based on Mendelian principles of inheritance [109]. This improvement program was focused on an ideotype characterized by precocity of fructification (beginning with the third year after germination, but with ≥0.5 kg of fruits per plant), high vitamin C content in fruit pulp (≥ 2.0 g per 100 g of fruit pulp), and larger fruits (fresh weight ≥ 10 g). The promoters of these programs touted that the first generation of genetically superior plants would be ready by 2010 and superior homozygous lines by 2016. Thus far, none of these goals have been achieved.

To overcome these drawbacks, a radical redefinition of ideotypes is necessary. Our current knowledge affords us the opportunity to create comprehensive ideotypes that is built upon detailed knowledge of plant genetics, biochemistry, physiology, anatomy, morphology, phenology, and ecology [113]. Additionally, including the state of the art technologies for multiomic data analysis (i.e., genomic, epigenomic, transcriptomic, proteomic, metabolomic, phenomic, etc.) will enable the rational design and application of innovative strategies for the domestication

and the genetic improvement program for camu camu. For example, using genome editing tools such as clustered regularly interspaced short palindromic repeats/associated protein-9 nuclease [CRISPR/Cas9 system], transcription activator-like effector nucleases [TALENs], and zinc finger nucleases [ZFNs] could be the molecular tools of choice to achieve the desired ideotypes [114–118], after obtaining the complete genome sequence of camu camu.

To accelerate the domestication and genetic improvement program to obtain *de novo* elite commercial varieties, the five-step strategy of genomics-based plant germplasm research recommended by Jia et al. [119] should be implemented: (1) the detection of genomic diversity in germplasm banks, (2) the conservation and protection of germplasm based on the knowledge of genomic diversity, (3) the use of diversity information to design a representative core collection, (4) the enhancement of germplasm banks using core collections, and (5) the discovery of new alleles and/or genes in the core collections.

To date, our research team has generated fruit transcriptome data and identified several of the genes involved in vitamin C biosynthesis that have proved to be polymorphic. For example, the D-mannose/L-galactose pathway mannose-1-phosphate guanylyltransferase (E.C. 2.7.7.13) contained >20 SNPs, GDP-mannose-3′,5′-epimerase (E.C. 5.1.3.18) had 13 SNPs, whereas L-galactono-1,4-lactone dehydrogenase (E.C. 1.3.2.3) only had 5 SNPs. The animal-like pathway UTP:glucose-1-phosphate uridylyltransferase (E.C. 2.7.7.9) contained 7 SNPs. In the uronic acid pathway pectin esterase (E.C. 3.1.1.11) and galacturan-1,4-alpha-galacturonidase (E.C. 3.2.1.15) showed more than 20 and 14 SNPs, respectively. Finally, in the ascorbate-glutathione pathway, the unigenes monodehydroascorbate reductase (E.C. 1.6.5.4) and glutathione reductase (E.C. 1.8.1.7) contained 2 and 3 SNPs, respectively [48]. It is likely that these mutations are associated with the high variation of vitamin C production reported between both individuals and populations of camu camu [13], as well as the differential gene expresssion and enzyme activities of the D-mannose/L-galactose pathway [120]. Our research group is currently finishing the transcriptome analysis of plantlets after germination and initial growth process and a draft genome sequence (using PacBio and Illumina technology) and annotation of camu camu. These forthcoming as well as previous functional and structural genomic resources will greatly accelerate the domestication process and the genetic improvement program of camu camu.

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