



Current Advances in Health Related Compounds in Sweet Cherry (*Prunus Avium* L.)

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Contents

1	Introduction: Sweet Cherries and Health	2
2	Chemical Composition	3
2.1	Sugar Content	3
2.2	Organic Acids and Total Acidity	4
2.3	Nitrogenous Compounds	5
2.4	Phenolic Compounds	5
3	Genetics and QTL Analyses	7
3.1	Sugar Content and Total Acidity	7
3.2	Fruit Color	8
3.3	Anthocyanins	9
3.4	Hydroxycinnamic Acids	10
4	Candidate Genes	11
4.1	Sugars and Organic Acids	11
4.2	Fruit Color and Anthocyanins	11
4.3	Hydroxycinnamic Acids	12

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5	Gene Expression and Functional Analyses	12
6	Future Prospects and Conclusions	14
	References	14

Abstract

Sweet cherry is a highly appreciated fruit by the consumer because of its attractiveness and flavor. But it is also a nutritious fruit and an excellent source of bioactive compounds associated with health benefits. These molecules include nitrogenous and phenolic compounds like melatonin, serotonin, anthocyanins, or hydroxycinnamic acids. Numerous studies have associated their consumption with health-related properties, such as blood pressure regulation, anti-inflammatory properties, or cancer prevention. The concentration of these compounds has been evaluated in several cultivars, and a wide range of variability has been reported, which has been used as a starting point for genetic and molecular studies that have allowed identifying QTLs and candidate genes associated with bioactive compound concentration. At the same time, more recent transcriptomic and metabolomic studies are providing light into understanding their regulation and role during fruit development. Agricultural and postharvest practices are also showing useful to improve bioactive content. In this chapter, most relevant results of these works are reviewed.

Keywords

Sweet cherry · *Prunus avium* · Bioactive compounds · Biofortification · Health

1 Introduction: Sweet Cherries and Health

Sweet cherry (*Prunus avium* L.) is a temperate climate fruit tree species with a high commercial value in national and international markets due to its attractive appearance, delicious taste, and rich nutritional value, which is related to the presence of vitamins, fiber, minerals, fatty acids, and sugars (Gonçalves et al. 2017; Serradilla et al. 2017). Additionally, sweet cherries contain other secondary metabolites with high biological value, like flavonoids such as anthocyanins, hydroxycinnamic and hydroxybenzoic acids, flavanones, flavonols, and flavan-3-ols (Ballistreri et al. 2013; Serradilla et al. 2016; Gonçalves et al. 2017; Martini et al. 2017). These compounds exhibit high antioxidant activity that helps in combating cell damage, reducing inflammation, and promoting overall health (McCune et al. 2011; Martini et al. 2017). Therefore, cherry consumption is linked to beneficial and health-promoting effects (Nawirska-Olszańska et al. 2017). Specifically, sweet cherry consumption exhibits a reduced risk of gout and arthritis attacks and a reduction in gout-related pain (Singh et al. 2015). On the other hand, it also exhibits other health-related properties linked to blood pressure reduction, body weight control, diabetes, and the prevention of degenerative diseases like Alzheimer's (Wu et al. 2014; Kent et al. 2016; Gonçalves et al. 2017). Additionally, the health effects of sweet cherry

consumption and its derivatives have focused on physiological aspects related to anti-inflammatory and anticancer activities, protection against cardiovascular diseases, anti-obesity and antidiabetic activities, and neuroprotective factors (Blando and Oomah 2019). Moreover, these beneficial effects of sweet cherries are associated with the anti-inflammatory capacity shown by anthocyanins, inhibiting the production of nitric oxide and other pro-inflammatory factors, as well as improving vision, brain function, and sleep quality (Tsuda 2012; Garrido et al. 2013). Additionally, the consumption of sweet and sour cherry has been associated with regulating the sleep-wake cycle, mood performance, sleepiness, and jet lag symptoms, thanks to molecules like melatonin (González-Gómez et al. 2009; Howatson et al. 2012). The use of biostimulants or elicitors, both preharvest and postharvest, with salicylic acid and its derivatives, methyl jasmonate, oxalic acid, and, recently, melatonin, has been found to increase the content of these bioactive compounds that can improve fruit quality and also bioactive capacity (Yao and Tian 2005; Giménez et al. 2014, 2015; Martínez-Esplá et al. 2014; Sharafi et al. 2021; Carrión-Antolí et al. 2022).

2 Chemical Composition

The scientific community has extensively studied the chemical composition of cherries (Usenik et al. 2008; Correia et al. 2017; Serradilla et al. 2017; Papapetros et al. 2018). Cherries are characterized by a low-calorie level (around 63.0 kcal [263.34 kJ] per 100 g), high water content (approximately 80%), and the absence of sodium (Serradilla et al. 2017; Gonçalves et al. 2017). Water content varies according to genotype and ripening stage, ranging from 75% offered by the late ripening cultivar ‘Starkrimson’ to 88% shown by the mid-season ripening cultivar ‘Sunburst’ (Gonçalves et al. 2021). Regarding inorganic matter or ash content, values from 0.44%, shown by the mid-season ripening cultivar ‘Skeena’, to 2.88%, measured by the early ripening cultivar ‘Burlat’, were reported (Gonçalves et al. 2021).

2.1 Sugar Content

One of the parameters that have the most significant influence on consumer acceptance is sweetness (Crisosto et al. 2003; Serradilla et al. 2016). This trait depends on the soluble solid content (SSC) and soluble sugars. This content is influenced not only by genotype but also by agronomic practices, climatic conditions of the production area, and even rootstock (Hrotko 2008; Usenik et al. 2010; Correia et al. 2017; Serradilla et al. 2017). A broad range of SSC has been reported in the literature depending on cultivar and geographic localization. In the northern hemisphere, this range varies from 11.9 °Brix in the cultivar ‘Celeste’ to 24.5, led by the cultivar ‘Salmo’ (Girard and Kopp 1998; Gonçalves et al. 2021). Similarly, in the southern hemisphere, values ranging from 16.8 (‘Santina’) to 23.9 °Brix (‘Bing’) have been described (Param and Zoffoli 2016). On the other hand, SSC tends to

increase during fruit ripening (Serradilla et al. 2012). Cherries are characterized by different soluble sugars, such as disaccharides like sucrose, maltose, and trehalose and monosaccharides or reducing sugars like fructose, glucose, and especially D-glucose (Serradilla et al. 2017; Chen et al. 2022). In addition, other sugars, or polyols, such as sorbitol, are also present in cherries (Blando and Oomah 2019). The glucose content ranges from 6 to 10 g/100 g of fresh weight (FW), while the fructose content ranges from 4.6 to 6.7 g/100 g of FW. These values are influenced by genotype, rootstock, soil, climatic conditions, and fruit ripening stage (Serradilla et al. 2017).

Like other stone fruits, the ripening process in cherries is characterized by a double sigmoid curve (Serrano et al. 2005), where three stages of development are identified. The first stage is mainly based on cell division and elongation when the fruit is entirely immature or green; the second stage is the endocarp hardening, which leads to the formation of the nucleus and fruit color appearance; the third stage is the period of exponential growth caused by cell enlargement, in which physiological and biochemical changes in sugar, organic acid, and color occur drastically (Blando and Oomah 2019; Chen et al. 2022). During this process, soluble sugars show a trend consistent with changes exhibited by SSC: an initial increase, followed by stabilization, and a further increase in the last stage of the ripening process (Chen et al. 2022). Generally, during ripening, disaccharides are cleaved into their monomers, such as glucose and fructose. The latter two tend to accumulate during fruit ripening, while sorbitol concentration does not show any significant changes at the end of ripening (Teribia et al. 2016; Serradilla et al. 2017; Chen et al. 2022). All these changes during fruit development result from the joint action of multiple metabolites and genes (Yang et al. 2021a).

2.2 Organic Acids and Total Acidity

The sweet cherry flavor is mainly defined by sweetness and sourness (Serradilla et al. 2017). Sourness is expressed as titratable acidity (TA), which depends on genotypes and ripening stages. In the sweet cherry germplasm, TA ranges from 0.48 ('Garnet') to 0.96%, shown by '4-84' and 'Sweetheart' cultivars (Gonçalves et al. 2021), reaching maximum values of TA at the end of the ripening process (Teribia et al. 2016). Cherries are generally considered medium acidity fruits, with pH ranging from 3.49 to 4.5 depending on cultivars and ripening stage (Ballistreri et al. 2013; Teribia et al. 2016; Gonçalves et al. 2021). Organic acids contribute to the flavor and pH of the fruits and, therefore, their sensory characteristics (Serradilla et al. 2017; Yang et al. 2021a). Among the primary organic acids found in cherries, malic acid, a predominant acid in the *Prunus* genus, stands out. Malic acid concentration depends on the cultivar and varies between 300 and 1100 mg/100 g of FW (Usenik et al. 2008; Serradilla et al. 2016); thus, some cultivars are more acidic than others. The following most crucial organic acids are citric acid, with values between 5 and 300 mg/100 g of FW, and succinic acid, which varies from 4 to 32 mg/100 g of FW (Serradilla et al. 2016). Other organic acids like oxalic, fumaric, and shikimic acid

have also been identified, showing concentrations below 8 mg/100 g of FW (Usenik et al. 2008; Serradilla et al. 2016). Like soluble sugars, malic acid content decreases at the beginning of ripening and then increases at the end of the process (Serrano et al. 2005). The balance of organic acids and sugars, defined by the SSC/TA ratio, affects cherry flavor and, consequently, customer acceptance (Crisosto et al. 2003; Serradilla et al. 2017). Gonçalves et al. (2021) found that this ratio ranged from 17.07 ('Sweetheart') to 32.33 ('Starkrimson'). However, Picota-type cultivars that show peduncle excision and late ripening time, like 'Ambrunés', can reach values close to 40 (Serradilla et al. 2012).

2.3 Nitrogenous Compounds

Cherries have also acquired great importance because their composition contains nitrogenous compounds of great bioactive value, such as indolamines, including melatonin (N-acetyl-5-methoxytryptamine), serotonin (5-hydroxytryptamine), and its precursor, the amino acid tryptophan. Within them, melatonin, a signaling molecule that regulates a wide range of physiological processes in plants and human circadian cycles, is a relevant compound in cherries (González-Gómez et al. 2009; Carrión-Antolí et al. 2022). Both melatonin and serotonin are synthesized from the essential amino acid tryptophan via the shikimic acid pathway. Similarly to other compounds, the melatonin and serotonin content depends on the cultivar and ripening stage of the fruits. For melatonin, concentration ranged from 0.6, shown by the Picota-type cultivar 'Pico Negro Limón', to 22.4 ng/100 g of FW of the early ripening cultivar 'Burlat'. Likewise, serotonin concentration ranges from 2.8 ('Pico Negro') to 37.6 ng/100 g of FW in 'Ambrunés'. Regarding the impact of the ripening stage, melatonin increased during ripening, while serotonin showed a less defined behavior (González-Gómez et al. 2009).

2.4 Phenolic Compounds

In addition to nitrogenous compounds, cherries, like other fruits, have acquired great importance in recent years due to the great content of bioactive compounds of phenolic nature that present high antioxidant activity against free radicals, which are related to beneficial properties for human health (Serra et al. 2011; Chockchaisawasdee et al. 2016; Correia et al. 2017; Serradilla et al. 2017; Blando and Oomah 2019; Gonçalves et al. 2021). The content of total phenols shown by cherries varies from 44.3 to 192 mg/100 g of FW depending on cultivar, ripening stage, and soil and climatic conditions (Serradilla et al. 2016). Among phenolic compounds present in cherries, flavonoids (anthocyanins, flavonols, and flavan-3-ols) and phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids) are the most abundant (Fig. 1) (Serra et al. 2011; Ballistreri et al. 2013; Serradilla et al. 2017). Within phenolic acids, cherries stand out for hydroxycinnamic acids, especially neochlorogenic and p-coumaroylquinic acids, although chlorogenic and

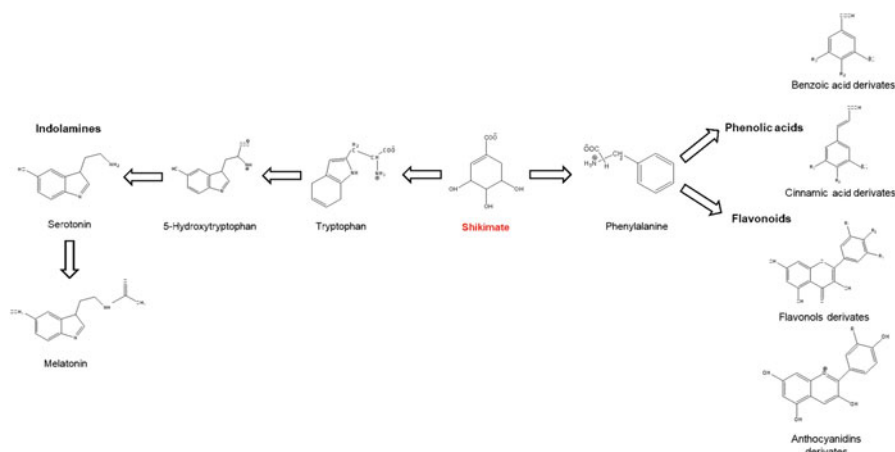


Fig. 1 Main phenolic compounds and indolamines present in sweet cherry fruits derived from shikimic acid (red) via different metabolic pathways

caffeoylquinic acids were detected in lower amounts (Serradilla et al. 2017). The concentration of these compounds is defined by genotype. For neochlorogenic acid, cultivars are classified based on concentration as low (4–20 mg/100 g of FW) like ‘Burlat’, ‘Lapins’, and ‘Sweetheart’; medium (20–40 mg/100 g of FW) like ‘Ferrovia’, ‘Blaze Star’, and ‘0900 Ziraat’; and high (40–128 mg/100 g of FW; ‘Bing’) (Ballistreri et al. 2013). For p-coumaroylquinic acid content, intervals from 0.77 (‘Lapins’) to 131.45 (‘Sam’) mg/100 g of FW were reported in the bibliography (Serradilla et al. 2016). Moreover, the ratio of these two primary hydroxycinnamic acids is characteristic of each genotype (Mozetič et al. 2006).

Among flavonoids, cherries stand out for their high content of anthocyanins. These pigments are responsible for skin and flesh color and, therefore, for one of the most critical organoleptic characteristics that define consumer purchase (Serradilla et al. 2017; Gonçalves et al. 2021; Carrión-Antolí et al. 2022). Anthocyanins are characterized as water-soluble pigments present in the vacuole. They have a basic structure called aglycone or anthocyanidin (flavylium 2-phenyl-benzopyrylium) to which one or more sugars are attached by glycosidic bonds forming anthocyanins (Serradilla et al. 2016). The main anthocyanin identified in cherry has been cyanidin 3-*O*-rutinoside followed by cyanidin 3-*O*-ruthinoside and, in lower concentrations, peonidin 3-*O*-rutinoside, peonidin 3-*O*-glucoside, pelargonidin 3-*O*-rutinoside, and delphinidin 3-*O*-rutinoside (Serra et al. 2011; Ballistreri et al. 2013; Serradilla et al. 2017; Gonçalves et al. 2021). The cyanidin 3-*O*-rutinoside represents between 77% and 96% of the total anthocyanins, with light-colored cultivars showing average anthocyanin values between 2 and 47 mg/100 g of FW, while dark cherries can reach up to 297 mg/100 g of FW (Serradilla et al. 2016). Anthocyanins tend to accumulate during fruit ripening (Serrano et al. 2005; Serradilla et al. 2011).

Other flavonoids present in cherries, considered as noncolored phenolic compounds, are flavonols, remarkably quercetin 3-*O*-rutinoside or rutin, which

concentration ranges from 1.84 ('Van') to 51.97 mg/100 g of FW led by cultivar 'Lapins' (González-Gómez et al. 2010; Martini et al. 2017). Rutin content also increases during fruit ripening (Serradilla et al. 2011). Recently, Gonçalves et al. (2021) identified other flavonols such as quercetin 3-*O*-hexoside, kaempferol 3-*O*-rutinoside, kaempferol hexoside (3-gluc), and the kaempferol hexoside derivative 2, with concentrations strongly influenced by genotype. Other flavonoids listed as noncolored phenolic compounds are flavan-3-ols. In cherries, mainly epicatechin and catechin have been identified but also polymeric procyanidin (Blando and Oomah 2019). These represent less than 11.29% of the total noncolored compounds (Gonçalves et al. 2021), and their ratio is strongly influenced by genotype (Serra et al. 2011). Cherries are notorious for their high epicatechin content compared to catechin content, although this ratio also varies depending on the cultivar (Serra et al. 2011). Epicatechin levels range from 0.43 to 13.38 mg/100 g of FW, while catechin content ranges from 2.92 to 9.03 mg/100 g of FW (Serradilla et al. 2016). However, in the case of polymeric procyanidins, found in a few cultivars, levels of 20 mg/100 g of FW have been described, as is the case of the cultivar 'Royal Ann' (Chaovanalikit and Wrolstad 2004).

3 Genetics and QTL Analyses

In the last decade, several quantitative trait loci (QTLs) determining the genetic variation of the most relevant agronomic and fruit quality traits have been identified in sweet and sour cherry (Sooriyapathirana et al. 2010; Zhang et al. 2010; Dirlwanger et al. 2012; Rosyara et al. 2013; Castède et al. 2014; Quero-García et al. 2014; Campoy et al. 2015; Cai et al. 2019; Quero-García et al. 2019, 2021; Calle et al. 2020, 2021; Calle and Wünsch 2020; Branchereau et al. 2022; reviewed in Quero-García et al. 2022). Most of these works focused on physical traits like size, weight, firmness, and color (Sooriyapathirana et al. 2010; Zhang et al. 2010; Rosyara et al. 2013; Quero-García et al. 2014; Calle et al. 2020; Calle and Wünsch 2020). Despite the variation of nutritional and health-related compounds is well documented in sweet cherries during harvest and postharvest, as described above, few studies have investigated the genetics or carried QTL analyses of these compounds in sweet cherries (Quero-García et al. 2019; Calle et al. 2021).

3.1 Sugar Content and Total Acidity

Three works have focused on the genetics of sugar content and acidity in sweet cherry (Zhao et al. 2014; Quero-García et al. 2019; Calle and Wünsch 2020). These studies investigated sugar content, evaluated as SSC using a refractometer, TA, and pH (the latter only in Quero-García et al. 2019). Zhao et al. (2014) used 3-year phenotypic data from 601 pedigree-related individuals that included F₁ seedlings, breeding parental and commercial cultivars in a combined way for QTL analyses. Two major QTLs were identified on linkage groups (LGs) 2 and 4, with a minor QTL

on LG7 for SSC. Quero-García et al. (2019) used an F_1 population ('Regina' $\times$ 'Garnet', $N = 117$) and 3-year data. This work identified SSC QTLs on LGs 1 and 3 by multi-year analysis, explaining from 6 to 10% of the variation. Later, in the multifamily QTL analysis conducted by Calle and Wünsch (2020), including 411 individuals from six populations of related pedigree and 2-year data, a major QTL for SSC, explaining nearly 30% of the phenotypic variation, was mapped on LG4. This QTL region overlapped with maturity and firmness QTLs on the same plant material. Also, a positive correlation among these traits was observed, with the latter maturing genotypes presenting a higher SSC value (Calle and Wünsch 2020). The results suggested the near presence of genes regulating sugar content and maturity, or genes with pleiotropic effects on these traits in this genome region (Calle and Wünsch 2020). In the same work, another minor SSC QTL was mapped on LG3, overlapping with the QTLs in the same region detected previously by Quero-García et al. (2019). For fruit acidity, high variability in QTLs detected between environmental years and populations was reported in these works, with QTLs on LGs 1, 2, 4, and 6 (Zhao et al. 2014; Quero-García et al. 2019; Calle and Wünsch 2020). Of them, only the genomic region at chromosome 6 seems stable across environments and plant materials for TA regulation in sweet cherry.

3.2 Fruit Color

Initial studies of the genetics of health-related compounds in sweet cherry were carried out indirectly by investigating fruit color. Sweet cherry color varies from yellow to mahogany or almost black, depending on the anthocyanin content profile (Gao and Mazza 1995; Jin et al. 2016; Calle et al. 2021). Fruit color was initially investigated as a relevant trait for sweet cherry breeding since different color fruits are preferred in different consumer markets (Crisosto et al. 2003). Furthermore, fruit color segregates in many breeding populations (Schmidt 1998). The cross of two red cultivars may result in blushed to dark cherries, and marker-assisted selection of this trait is desirable for breeders. By analyzing color segregation in sweet cherry progenies, the earliest studies showed that fruit skin color is determined by a major gene, in which alleles for red color are dominant to yellow or blushed (Fogle 1958; Schmidt 1998). The presence of minor genes exhibiting the epistasis effect was also proposed. More recently, research on the genetic control of skin and flesh color in sweet cherry by QTL analyses was carried out by Sooriyapathirana et al. (2010). In this work, fruit and skin color QTLs were mapped using a progeny from a cross of two cultivars with different flesh and skin color, blush-skinned and yellow-flesh 'Emperor Francis' and dark mahogany-skinned and red-fleshed 'New York 54' (Sooriyapathirana et al. 2010). The QTL analysis was conducted in 190 individuals that were phenotyped using a colorimeter, through a pseudo-testcross mapping strategy of a consensus map of 198 markers (102 SSR, 61 AFLP, 28 gene-derived markers, and seven SNP; Olmstead et al. 2008). A major QTL, explaining a large percentage of the phenotypic variation for skin and

flesh color, was identified on LG3. Also, minor QTLs were reported on LGs 6 and 8. This work confirmed that sweet cherry color was determined by a major regulatory gene (Sooriyapathirana et al. 2010). In a later study focused on deciphering the molecular mechanisms regulating fruit color, Jin et al. (2016) also mapped skin color using another sweet cherry F₁ segregating population. In this population ('Wanhongzhu' × 'Lapins'), both parents are dark red, and a 3:1 (dark red and bluish fruits) segregation was observed for the 465 hybrids, confirming the regulation model by a major gene with dominance for dark red. In this case, specific-locus amplified fragment (SPAF) markers were used, and fruit color was mapped at a narrowed QTL (70.4–70.5 cM) on LG3. More recently, Calle et al. (2021) mapped skin and flesh color QTLs using 161 individuals of an F₁ population derived from the cross 'Vic' × 'Cristobalina' and genotyped with the RosBREED Cherry 6 + 9 K Illumina Infinium[®] SNP array (Vanderzande et al. 2020). The QTL analysis, using genetic maps of 910 ('Vic') and 789 ('Cristobalina') single nucleotide polymorphisms (SNPs) (Calle et al. 2021), also revealed a major QTL region for sweet cherry color on the same LG3 region previously reported by Sooriyapathirana et al. (2010) and Jin et al. (2016). This QTL region corresponds to chromosome 3, between 9.3–13.5 Mbp in *Prunus avium* v1.0.a1 (Shirasawa et al. 2017) and 11.1–15.4 Mbp of *Prunus avium* Tieton v1.0 genome (Wang et al. 2020). An additional minor QTL for flesh color was identified on LG4, explaining 15% of phenotypic variation when colorimeter data was used for QTL mapping (Calle et al. 2021).

3.3 Anthocyanins

QTL analyses of anthocyanin content in sweet cherry were also carried out by Calle et al. (2021) in the same work as previously reported for skin and flesh color QTLs. Anthocyanin compounds were extracted and quantified by high-performance liquid chromatography (HPLC) from 15 mature fruits of each progeny hybrid. Four anthocyanins (cyanidin 3-*O*-glucoside, cyanidin 3-*O*-rutinoside, peonidin 3-*O*-glucoside, and peonidin 3-*O*-rutinoside) were identified and quantified. The use of these data for QTL mapping revealed the most significant QTLs for the four anthocyanins on the same genomic region of chromosome 3 (Fig. 2) where fruit color had been mapped by Sooriyapathirana et al. (2010), Jin et al. (2016), and in the same population (Calle et al. 2021). The percentage of phenotypic variation explained by these QTLs ranged from 12 to 23%, and these results confirmed fruit color and anthocyanin biosynthesis have the same genetic determinants. In addition to this main QTL region on LG3, other minor anthocyanin content QTLs were also mapped on LG7 for cyanidin 3-*O*-glucoside, cyanidin 3-*O*-rutinoside, and peonidin 3-*O*-glucoside explaining up to 10% of phenotypic variation and on LG4 for peonidin 3-*O*-rutinoside (Fig. 2) in the same region where a color QTL was also mapped in the same population (Calle et al. 2021). These results indicate that beyond a major gene in chromosome 3, other genes in chromosomes 4 and 7 also contribute, to a lesser extent, to anthocyanin content regulation in sweet cherry.



Fig. 2 Physical position in the *Prunus avium* L. genome ('Tieton' v2.0; Wang et al. 2020) of QTLs (Sooriyapathirana et al. 2010; Jin et al. 2016; Calle et al. 2021) associated with health-related (HR) compounds identified in the species. Fruit color QTLs (*qP-Color*) are shown in red, anthocyanin content QTLs (*qP-CyG*, cyanidin 3-O-glucoside; *qP-CyR*, cyanidin 3-O-rutinoside; *qP-PeG*, peonidin 3-O-glucoside; and *qP-PeR*, peonidin 3-O-rutinoside) in orange, and hydroxycinnamic acid QTLs (*qP-NA*, neochlorogenic acid; *qP-CQA*, *p*-coumaroylquinic acid; *qP-CA*, *p*-coumaric acid) in green. Position of candidate genes associated with HR-compound biosynthesis (*C3H*, coumarate 3-hydroxylase and *MYB10*) are also included (Sooriyapathirana et al. 2010; Calle et al. 2021). Physical position of Pav-Rf-SSR marker for fruit color prediction is also included (Sanderful et al. 2016)

3.4 Hydroxycinnamic Acids

The genetics of hydroxycinnamic acid content was also investigated in sweet cherry by Calle et al. (2021). Three compounds, neochlorogenic acid, *p*-coumaroylquinic acid, and *p*-coumaric acid, were also detected and quantified by HPLC and analyzed for QTL mapping using the same population and maps as for color and anthocyanin content in Calle et al. (2021). In this case, a major QTL was detected at the bottom region of LG1 (Fig. 2) for the three compounds (141.34–141.63 cM; 46.67–47.17 Mbp in the peach genome v2.0.a1). These QTLs were highly significant (logarithm of the odds: LOD > 20) and explained a substantial percentage of the phenotypic variation (60–78%; Calle et al. 2021). Other less significant QTLs were found on LGs 3, 4, 5, and 6. These were associated with minor variations in the concentration of these compounds (4–11% of phenotypic variation). Similarly, two additional minor QTLs for *p*-coumaroylquinic acid and *p*-coumaric acid were found on the same region of LG2

(Fig. 2) (2.24–6.09 Mbp; peach genome v2.0.a1) (Calle et al. 2021). The results of this work showed that a major gene also regulates the concentration of these compounds and is likely located at the bottom of chromosome 1.

4 Candidate Genes

4.1 Sugars and Organic Acids

Genetic regulation of sugars and organic acids in cherries remains largely uncharacterized. Only a few studies investigated changes during fruit development related to the biosynthesis of these compounds (Beaver et al. 1995; Gao et al. 2003; Yang et al. 2021a). Initial studies in sour cherry revealed two *sorbitol transporter* genes (*SOT1* and *SOT2*) that were expressed during fruit development playing a major role in sorbitol accumulation in the species (Gao et al. 2003). In a more recent study by Yang et al. (2021a), transcriptomic analysis during the fruit development period of the sweet cherry cultivar ‘Black Pearl’ revealed genes like *SOT*, *PFK* (phosphofructokinase), *NINV* (neutral invertase), or *SUS* (sucrose synthase) highly upregulated during early stages of fruit development and another set of genes like *PGI* (phosphoglucosomerase), *UGP* (UDPG-pyrophosphorylase), *PGM* (phosphoglucomutase), and *SPS* (sucrose-phosphate synthase) upregulated during the late stage of fruit development when sucrose accumulation was enhanced. Six additional genes of the *SWEET* family were identified, showing different expression patterns related to sugar transports (Yang et al. 2021a). Regarding organic acids, just a few genes like *PEPC* (phosphoenolpyruvate carboxylase) and one *MDH* (malate dehydrogenase) that were downregulated during fruit development were observed to keep acid content low by decreasing malate acid during cherry development (Yang et al. 2021a). In this same study, other genes responsible for the metabolism of organic acids like *GOGAT* (glutamate synthase) and *GDH* (glutamate dehydrogenase) increased their expression during fruit development, reaching the highest transcription close to harvest time (Yang et al. 2021a).

4.2 Fruit Color and Anthocyanins

Most of the genetic and molecular studies involving health-related compounds in sweet and sour cherries focused on anthocyanin content regulation. Transcription factors (TFs) are known to be critical regulators of anthocyanin biosynthesis in cherries (Lin-Wang et al. 2010; Jin et al. 2016; Chen et al. 2022). The complexes of TFs containing an R2R3 MYB, a WD40, and a basic helix-loop-helix (bHLH) were observed in other species to promote anthocyanin accumulation through binding to genes involved in the flavonoid pathway (Allan et al. 2008). In sweet cherry, various studies indicated that the R2R3-MYB TF *PavMYBA/PavMYB10* interacts with two other TFs (*PavbHLH3* and *PavWD40*) to form an MBW complex (MYB-bHLH-WD40) that regulates the expression of two key genes associated with the

anthocyanin pathway (*PavANS* and *PavUFGT*) (Shen et al. 2014; Starkevič et al. 2015; Jin et al. 2016; Guo et al. 2018). This MYB TF (*MYB10*) is located at the primary color, and anthocyanin QTLs reported in sweet cherry chromosome 3 (Sooriyapathirana et al. 2010; Jin et al. 2016; Calle et al. 2021), supporting its relevance. This transcription factor was first cloned by Lin-Wang et al. (2010) in sweet and sour cherry. Based on additional expression analysis by qPCR, a clear correlation between anthocyanin content and gene expression was confirmed (Lin-Wang et al. 2010). Later works found the same correlation in the dark red cultivar ‘Hong Deng’ (Shen et al. 2014). These studies confirmed *PavMYB10* as one of the key genes associated with variation in flavonoid content in the species, and it was the basis for developing a DNA test (Pav-Rf-SSR) to predict fruit color in sweet cherry (Fig. 2) (Sanderful et al. 2016). Additionally, various alleles for *PavMYB10* were associated with different ranges of flavonoid accumulation and fruit coloration in sweet cherry (Sooriyapathirana et al. 2010; Jin et al. 2016). Other TFs belonging to 22 different families, specifically bZIP, C2C2-Dof, NAC, bHLH, and R2R3-MYB, were also observed to mediate in anthocyanin regulation in response to light in the ‘Rainier’ cultivar (Guo et al. 2018).

4.3 Hydroxycinnamic Acids

The study by Calle et al. (2021) suggested a candidate gene for the regulation of the main hydroxycinnamic acid content in sweet cherries. The gene, *p-coumarate 3-hydroxylase* (*C3H*), located within LG1 QTL confidence interval identified in the same work, was considered the strongest candidate gene for hydroxycinnamic acid regulation in sweet cherry (Calle et al. 2021). This enzyme was previously observed in other species and is involved in the hydroxycinnamic acid biosynthesis pathway (Chagné et al. 2012; Kim et al. 2019). The LG1 region in which sweet cherry had the most significant QTLs for hydroxycinnamic acids was found to be syntenic to LG15 in apple (Illa et al. 2011), where also a major QTL for hydroxycinnamic acid content had been identified in apple (Chagné et al. 2012), leading to the identification of this candidate gene by Calle et al. (2021) and suggesting a common mechanism for the regulation of these phenolic acids.

5 Gene Expression and Functional Analyses

In sweet and sour cherry, strong correlations between the expression of structural and regulatory genes have been associated with health-related compound biosynthesis pathways (Lin-Wang et al. 2010; Liu et al. 2013; Shen et al. 2014; Starkevič et al. 2015; Wei et al. 2015; Guo et al. 2018). Within health-related compounds, anthocyanin biosynthesis was the widest studied in cherries. These compounds are synthesized through the flavonoid pathway (Winkel-Shirley 2001), in which most of the genes related to the regulation and biosynthesis of anthocyanins are well characterized in model plants (Allan et al. 2008). Initial studies were conducted to find candidate genes associated with anthocyanin biosynthesis in cherries by real-time PCR (RT-PCR)

targeting some candidate genes reported in other species. Lin-Wang et al. (2010) analyzed the expression level of two genes (anthocyanidin synthase [*ANS*] and chalcone synthase [*CHS*]) potentially involved in the anthocyanin biosynthesis pathway through RT-PCR. Two cultivars, ‘Stella’ (red coloration) and ‘Rainier’ (bicolor coloration), were used for comparison of expression profiling during fruit development, in which expression of *ANS* and *CHS* genes showed upregulation correlated with anthocyanin content (Lin-Wang et al., 2010). Similarly, the expression level of six anthocyanin biosynthesis genes (*ANS*, *CHS*, chalcone isomerase [*CHI*], flavanone 3-hydroxylase [*F3H*], dihydroflavonol 4-reductase [*DFR*], and UDP glucose: flavonol 3-O-glucosyltransferase [*UFGT*]) was analyzed by RT-PCR in high-anthocyanin-content cultivars (‘Hongdeng’ and ‘Caihong’ by Liu et al. (2013); ‘Kitayanka’, ‘Irema BS’, ‘Werdersche braune’, and ‘Belobokaya rannyaya’ by Starkevič et al. (2015)). In these studies, as previously reported by Lin-Wang et al. (2010), all investigated gene expression manifested a significant correlation with anthocyanin content, in which the expression level of these genes increases through fruit development.

Whole genome transcriptome analyses have complemented these findings. Wei et al. (2015) sequenced and annotated a reference transcriptome of sweet cherry to identify genes associated with anthocyanin biosynthesis. In this study, they sampled total anthocyanin content during four stages of fruit development (from 20 to 55 days after pollination) and sequenced the transcriptome of yellow (‘13–33’) and dark red (‘Tieton’) cultivars for comparison. The biological pathway analysis of these transcripts revealed 72 genes related to anthocyanin biosynthesis during fruit development, including key genes like *ANS*, *CHS*, *CHI*, *F3H*, *DFR*, *UFGT*, phenylalanine ammonia-lyase (*PAL*), 4-coumarate-CoA ligase (*4CL*), and flavanone 3'-hydroxylase (*F3'H*) involved in anthocyanin pathway (Wei et al. 2015). As observed in the RT-PCR studies, these genes were highly upregulated in the dark red cultivar (‘Tieton’) and downregulated in the yellow fruits of ‘13–33’ (Wei et al. 2015). Guo et al. (2018) also performed RNA sequencing (RNAseq) analysis of anthocyanin biosynthesis in sweet cherry to investigate the anthocyanin accumulation mechanism further. The transcriptomes of two contrasting cultivars, ‘Hongdeng’ (dark) and ‘Rainier’ (bicolor), were sequenced during fruit development, and as observed in previous studies in cherries (Starkevič et al. 2015; Wei et al. 2015; Shen et al. 2014; Lin-Wang et al. 2010), genes encoding enzymes like *CHS*, *CHI*, *F3H*, and *F3'H* were significantly upregulated in dark fruits. Similarly, results were reported by Yang et al. (2021b) in which weighted gene co-expression network analysis (WGCNA) indicated similar expression patterns of *4CL2* and *ANS* with 11 TF (*bHLH13/74*, *DIV*, *ERF109/115*, *GATA8*, *GT2*, *GTE10*, *MYB308*, *PosF21*, and *WRKY7*). Additionally, another set of genes related to hormone and light signaling, like *protein phosphatase 2Cs*, *PHYTOCHROME INTERACTING FACTOR 3 (PIF3)*, *phytochromes*, and *ELONGATED HYPOCOTYL 5 (HY5)*, were also significantly differentially expressed between dark- and light-colored fruits and therefore associated with anthocyanin biosynthesis (Guo et al. 2018). Together, gene expression analyses have shown significant differences in transcript accumulation between cultivars with high and low anthocyanin accumulation, which are especially significant in expression for *UFGT* and *CHS* (Shen et al. 2014; Starkevič et al. 2015; Wei et al. 2015).

In addition to the genes directly involved in the anthocyanin pathway, various studies suggested that genes related to the signaling pathways of phytohormones like abscisic acid (ABA) and gibberellic acid (GA) play essential roles in the accumulation of health-related compounds (Sun et al. 2010; Jia et al. 2011; Guo et al. 2018; Chen et al. 2022). Shen et al. (2014) reported that silencing a gene (*PavNCED1*) essential for ABA biosynthesis (Zhang et al. 2009) blocked anthocyanin biosynthesis in sweet cherry, suggesting a complex interaction of genes regulating anthocyanin pathway beyond enzymes involved in the flavonoid pathway. In the same way, Guo et al. (2018) identified 32 genes required for plant hormone biosynthesis that were regulated in response to light exposure. In this study, differentially expressed genes related to ABA, GA, auxin, and ethylene pathways were modulated by light, being ABA and GA the only phytohormones that correlated with expression profiles of *HY5* and *PIF3* genes, suggesting that ABA and GA might be the main light-dependent hormones associated with anthocyanin biosynthesis (Guo et al. 2018).

6 Future Prospects and Conclusions

The works reviewed here show that sweet cherries are a health-valuable fruit, which is also highly appreciated by consumers, including children, making them an excellent source of health-related compounds. Therefore, it is important that the healthy quality of sweet cherries is known and communicated so it can be further consumed and produced. At the same time, sweet cherries are highly perishable and seasonal, which complicates their availability throughout the year and to markets far from the cultivation area. Agronomic practices, breeding, and postharvest technology research are allowing to improve these drawbacks, and sweet cherry production, quality, and availability (in time and space) have largely improved in the last years. Extensive efforts are being made in these areas, which have resulted in remarkable improvement, but it is essential not to lose the healthy qualities of sweet cherry in the way. In fact, breeding for a healthier cherry is still lacking, and a more extensive evaluation of HR compounds in sweet cherry collections would be needed. As healthy nutrition is more evident every day and society more aware of it, it is necessary to move forward to obtain a healthier fruit, if possible, or a designed fruit that can help mitigate diet deficiencies or fight specific diseases. The availability of new technologies will help to move forward in this direction. In this sense, agronomic and postharvest practices are useful in improving sweet cherries' health qualities.

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