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Review

Grape Tartaric Acid: Chemistry, Function, Metabolism, and Regulation

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Abstract: Tartaric acid (TA) is the primary organic acid present in grapes and a fundamental constituent of wine, responsible for shaping its taste, aroma, and overall quality. This review presents a comprehensive overview of the advances made in previous investigations on grape tartaric acid. It elucidates the structural properties, distribution characteristics, biosynthesis, catabolism, and transcriptional regulation of grape tartaric acid, and also speculates on the regulatory mechanism of tartaric acid based on the modulation of ascorbic acid-related transcription factors. Furthermore, this review provides insights into the future research directions and objectives, with the goal of providing a reference for the analysis of the complete biosynthetic pathway of grape tartaric acid, thereby enabling precise regulation of tartaric acid.

Keywords: grape; tartaric acid; ascorbic acid; metabolism; regulation

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1. Introduction

Grapes (*Vitis vinifera* L.) are one of the oldest fruit crops globally, with the broadest cultivation history, largest planting area, and highest economic value. Grape fruits are used for various purposes, including fresh consumption, juice extraction, drying, and wine production, with rich nutritional value. China ranks first in grape production globally (FAO, 2021), which is currently transitioning from a focus on total growth to a more quality-oriented approach to production [1,2]. Grapes are one of the four major fruit crops with high adaptability to diverse soil and climatic conditions, early fruiting, high yield efficiency, and ease of cultivation, making it a popular choice among cultivators. Malic acids (MA) and tartaric acids (TA) are recognized as the primary organic acids in grape fruits, with TA serving as a distinctive feature of grapes, accounting for 42.8–77% of the organic acid content [3]. Therefore, TA is considered the fundamental component of grape fruit.

TA is a vital contributor to the acidity of the wine, which is not very strong, refreshing, and firm. In addition, it is relatively stable and remains unmetabolized during the winemaking process [4]. TA contributes to the unique flavor and low pH of the wine, thereby determining its resistance to spoilage, microbial stability, and aging potential. Despite the accumulation of TA being less susceptible to environmental influences, little is known about its synthesis in grape tissues and its exact location.

Grape varieties with a high concentration of TA are deemed suitable for winemaking due to their ability to enhance color stability, prevent oxidation, and inhibit spoilage [5]. Conversely, grape germplasm with low TA results in dull and thin wine that is susceptible

to cloudy wines. Hence, achieving an optimal increase in organic acid content is essential in the winemaking process to produce wines that are full-bodied and smooth [5,6]. However, with the rise in temperatures caused by global warming, the acidity of wine grapes is decreasing. As a result, there is an increase in the pH of both the juice and the fermented wine, which can lead to a deterioration of microbial homeostasis. Thus, it needs more SO_2 additions to effectively inhibit the growth of harmful microorganisms, but it will lead to excessive SO_2 content in wine, affecting the flavor and aroma of wine [7]. To enhance fermented wine acidity and restore microbial homeostasis, winemakers often need to add significant amounts of tartaric acid during the winemaking process. This addition serves the purpose of regulating pH and TA levels, ultimately ensuring the desired quality of the wine [8,9]. The artificial addition of TA to maintain the acidity of wine increases the production cost of wineries. Therefore, the endogenous TA content of grapes plays a vital role in the quality of the wine. Grapes accumulate a large amount of TA during fruit development, prolonging hanging fruit time, promoting sugar accumulation, and increasing flavor substances while also enhancing wine stability and taste.

Drawing on current research progress on tartaric acid biosynthesis, catabolism, and transcriptional regulation in grapes, this review aims to provide an overview of the latest advances in TA accumulation in grape berries. Furthermore, we discussed in detail the regulation of several key enzymes involved in the biosynthesis of TA and precursor ascorbic acid. This study not only summarizes the factors that influence tartaric acid accumulation, such as temperature, light, growth regulators, rootstock, grape training systems, and regulation of transcription factors, but also analyzes these factors to gain a better understanding of their impact on TA accumulation. Despite the crucial role of endogenous tartaric acid (TA) in wine grapes and winemaking, there is still a lack of understanding regarding its biosynthesis and accumulation. Therefore, this review will delve into the literature on TA biosynthesis and its biochemical and agronomic effects on accumulation, focusing on providing insights into the synthetic pathways and biological regulatory mechanisms of TA in developing grape berries.

2. Characteristics of TA

2.1. Structure and Properties

Tartaric acid (TA) is a dicarboxylic acid with the molecular formula $C_4H_6O_6$, also known as 2,3-dihydroxysuccinic acid or grape acid. In its unpurified form extracted from grapes, it exhibits its natural color, while purified TA appears as a white crystalline powder [10]. The acidity of TA is approximately 1.2 to 1.3 times higher than that of citric acid (CA) at the same concentration [3]. Tartaric acid is soluble in both water and ethanol. In grapes, the accumulated TA is primarily L-(R,R)-(+)-tartaric acid, which is also known as dextrotartaric acid. The mirror image, enantiomeric form is D-(S,S)-(-)-tartaric acid, or laevotartaric acid. TA can also exist in an optically inactive form called meso-(R, S)-tartaric acid, or mesotartaric acid (Figure 1). Another optically inactive form is DL(S,S/R,R)-(-)-tartaric acid, which is a 1:1 mixture of the laevo and dextro forms, known as racemic acid or paratartrate [10]. Organic acids play a crucial role in the wine aging process [11], and among them, TA is the most dominant one. TA levels are known to be less sensitive to climatic conditions during grape ripening [12]. A higher concentration of TA in grapes is associated with better resistance to the effects of climate change. However, it is important to note that climate change can also have a significant impact on the concentration of various organic acids in grapes [13,14].

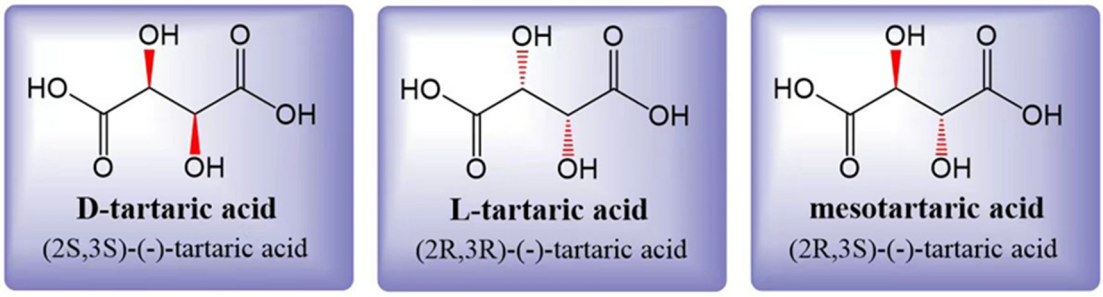

Figure 1. Three structural formulas for tartaric acid: laevotartaric acid (D-tartaric), dextrotartaric acid (L-tartaric), and mesotartaric acid. The dextro- and laevo- prefixes identify the (+) and (-) forms, respectively. Figure modified from [10].

2.2. Distribution and Transportation of TA

TA is primarily found in the form of potassium salt in a diverse range of plants and fruits, with only small amounts present in its free state. The accumulation of TA is known to occur during the early stages of leaf and berry development, with limited biosynthesis occurring in other tissues and mature berries [15]. In grape berries, TA levels (TA content measured in grams) gradually increase during fruit growth and development, peaking during veraison, and then decrease during the ripening process. This accumulation pattern is similar to that observed for other organic acids. The content of TA in grapes varies depending on the genotype, with wine grape varieties generally exhibiting higher TA content than fresh grapes [16].

Early research has suggested that tartrate mainly originates from leaves [17]. Currently, available studies indicate that besides grape leaves, leaves from approximately 15 other species listed in Buch's bibliography of *Organic Acids in Higher Plants* also contain TA [18]. While tartrate can be found in microscopic amounts in widely distributed angiosperms, it accumulates significantly only in three different families: Vitaceae, Geraniaceae, and Leguminosae [18]. A conducted study exposed grapevine leaves to $^{14}CO_2$ light and dark conditions for different durations, followed by radio labeling, and found that TA is present in the leaves at four times the concentration of MA [19]. Moreover, it has been suggested that leaves are the primary site of TA synthesis in grapes, and the accumulation of TA in grape berries is derived via translocation [20,21].

The organic matter is synthesized by leaves through photosynthesis, which is then decomposed, supplied, and stored in the form of sucrose in berry pre-veraison. A proportion of sucrose is converted into fructose and glucose to participate in glycolysis during respiration. Sucrose subsequently becomes the primary raw material for ATP synthesis, allowing for the synthesis of tartaric acid in berries. Organic acids are primarily transported across the tonoplast in plants. For example, malate and citrate accumulate in plant cells due to their complex metabolism and vacuolar storage and are transported into the vacuole occurring by facilitated diffusion [22,23]. Facilitated diffusion is the primary mode of transport of organic acids from the cytosol to the vacuole; this transportation process is mediated mainly by channels, carriers, and proton pumps [24]. Research has shown that AsA, a monovalent anion at physiological pHs, is unable to permeate membranes and must be transported through chloroplasts, apoplasts, and vacuoles [25]. Previous studies have detected AsA in the phloem of various crops such as barley, peas, potatoes, tobacco, and turnips [26]. Burbidge (2021) et al. believed that AsA is transported through the phloem to the leaves and fruits [8]. It is believed that the biosynthesis of TA occurs in the cytoplasm and this hypothesis is supported by the fact that the cytoplasm contains high concentrations of AsA [27]. Moreover, L-Idonate dehydrogenase (L-IdnDH) is the only known enzyme of the TA biosynthetic pathway in grape berries, which is distributed mainly in the vacuole (immature berries) and cytoplasm (mature berries) [28]. On the other hand, Ford et al. (2012) claimed the accumulation of TA occurs in the vacuoles of mature berries, which is synthesized starting from the earliest stages of berry formation and continuing

until 40–50 days after flowering [29]. Hence, the distribution of TA is closely related to berry maturity. In immature berries, TA is mainly synthesized in the cytoplasm, while in mature berries, it is primarily stored in the vacuole. Again, it is believed that AsA is the precursor of TA synthesis, the accumulation of TA in the vacuole is related to the transport of AsA, and the biosynthesis of AsA in leaves and its eventual transport to grape berries provide a regulatory process for the location and timing of TA synthesis in grapes.

3. The Biosynthetic Pathway of TA

Table fruits are typically rich in AsA, but grapes do not accumulate large amounts of it as it is used as a precursor for the synthesis of TA [30]. While there is interest in the accumulation of TA in grapes, few mechanisms are known for the regulation of TA concentration. The three pathways of TA biosynthesis in higher plants are AsA C4/C5, AsA C2/C3, and 5-keto-D-gluconate C4/C5 sites cleavage leading to TA formation [8]. In grape berries, AsA is cleaved between C4 and C5 to form 2-keto-L-gulonic acid (2KGA), which is then converted to L-Idonic acid, followed by 5-keto-D-gluconic acid (5KGA), L-Threo-tetruronate acid, and, ultimately, converted into TA [29]. The synthetic pathway of TA in rose-scented geranium (*Pelargonium* sp.) involves the cleavage reaction of ascorbic acid C2 and C3 to generate oxalic acid (OA) and threonic acid, followed by conversion of threonic acid to TA [31]. There are two distinct stages of TA biosynthesis in grape berries: the synthesis of AsA, the precursor of TA, and the synthesis of TA (Figure 2).

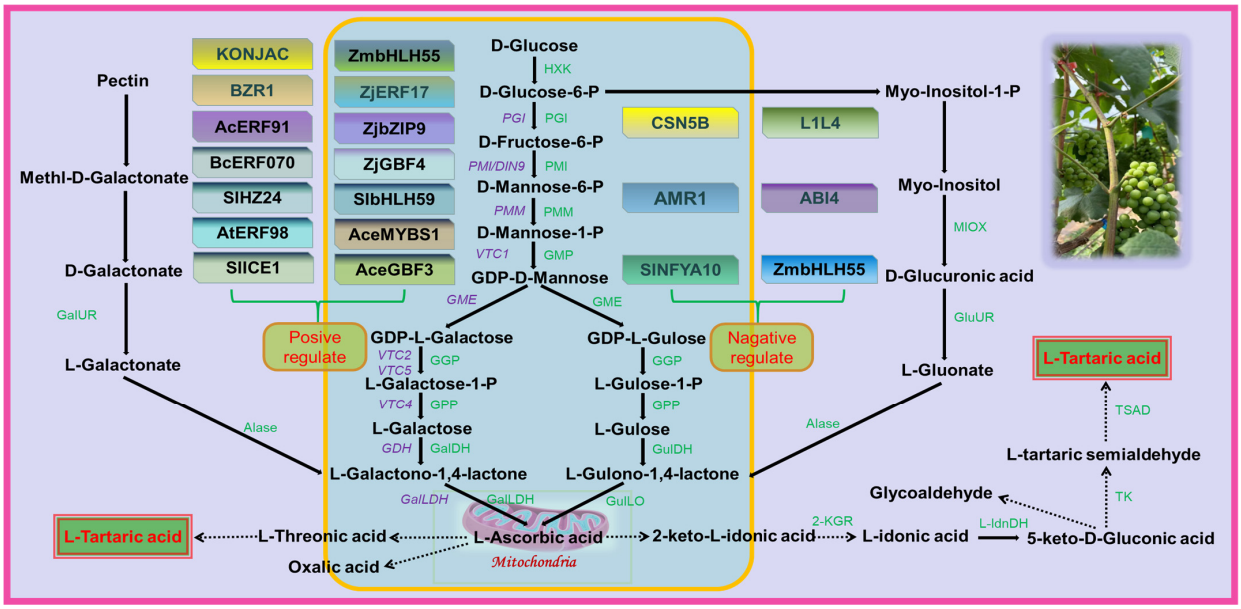

Figure 2. Grape involved in tartaric acid biosynthesis pathway. HXK, Hexokinase; PGI, Glucose-6-phosphate isomerase; PMI, Mannose-6-phosphate isomerase; PMM, Phospho mannomutase; GMP, GDP-Mannose pyrophosphorylase; GME, GDP-D-mannose-3′, 5′-epimerase; GGP, GDP-L-galactose phosphorylase; GalDH, L-galactose dehydrogenase; GulDH, L-gulose dehydrogenase; GulLO, L-Gulono-1,4-lactone oxidase; GalLDH, L-galactono-1,4-lactone dehydrogenase; GalUR, D-galacturonate reductase; GluUR, D-glucuronate reductase Alase, Aldonolactonase; MIOX, Myo-inositol oxygenase; 2-KGR, 2-keto-L-gulonate reductase; L-IdnDH, L-Idonate dehydrogenase; TK, Transketolase; TSAD, Tartaric semialdehyde dehydrogenase. The solid lines in the figure indicate that the pathways are confirmed and the dashed lines indicate that they are unconfirmed. The figure identifies several transcription factors that are involved in regulating the biosynthesis of AsA. Some transcription factors, such as SlICE1, AtERF98, SlHZ24, and BZR1, have been shown to have a positive effect on AsA biosynthesis. On the other hand, other transcription factors, including SlNFYA10, ABI4, CNSN5B, ZmbHLH55, AMR1, and L1L4, have a negative regulatory effect on AsA biosynthesis. Figure modified from [30,32,33].

3.1. AsA Biosynthesis Stage

There are several proposed pathways for AsA synthesis in plants, of which the L-galactose pathway is the predominant one in plants [32] and also an important pathway in grape berries [33], while alternative pathways for AsA have been proposed, including the L-gulose pathway [34], D-galacturonate pathway [35], and myo-inositol pathway [36]. In the L-galactose pathway, GDP-D-mannose is catalyzed by GDP-mannose-3′,5′-differential isomerase (GME) to produce GDP-L-galactose, which is then converted by GDP-L-galactose phosphorylase (VTC2) into L-galactose-1-P. L-galactose is then generated by L-galactose-1-P-phosphorylase (VTC4) before being dehydrogenated by L-galactate dehydrogenase (L-GalDH) to produce L-galactono-1,4-lactone, which is the immediate precursor of AsA. Finally, L-galactono-1,4-lactone is catalyzed by L-galactono-1,4-lactone dehydrogenase (L-GalLDH) to generate AsA [37,38].

3.2. TA Biosynthesis Stage

Based on previous research, it is postulated that the biosynthesis of TA in plants involves the hydrolysis and oxidation of AsA to 2-KGA, which is subsequently reduced to L-Idonic acid by the enzyme 2-keto-L-gulonic acid reductase (2-KGR). L-Idonic acid is then oxidized by L-Idonic acid dehydrogenase (L-IdnDH) to 5-KGA, which is cleaved between C4 and C5 to form 4-carbon L-threo-tetruronate. This compound is further oxidized to yield TA [39]. However, the specific enzymes involved in the biosynthesis of TA in plants, including the functions of transketolase (TK) and tartaric acid semialdehyde dehydrogenase (TSAD) in the grapevine TA synthesis pathway, remain unverified and require in-depth investigation.

4. Key Enzymes in TA Biosynthesis Pathway

Currently, most of the enzymes in the stage of AsA biosynthesis have been validated, whereas the functions of key enzymes in the stage of TA biosynthesis are still uncertain. Cruz-Rus et al. (2010) identified and characterized the expression of several genes, namely D-galacturonide reductase (GalUR), myo-inositol oxidase (MIOX), GDP-D-mannose pyrophosphorylase (GMP), GDP-D-mannose-3,5-epimerase (GME), and L-galactose-1,4-lactone dehydrogenase (L-GalLDH) from grape berries [33]. Wheeler et al. (1998) demonstrated the presence of L-galactose dehydrogenase in higher plants, which oxidizes L-galactose to L-galactose-1,4-lactone, and, eventually, AsA, and detected GDP-mannose-3′,5-differentiated isomerase activity in extracts of pea embryonic axes and ammonium-sulphate precipitates from A. thaliana leaves [32]. Jia et al. (2019) identified aldo-keto reductase (Vv2KGR) in *V. vinifera* with 2-keto-L-gulonic acid reductase activity, which efficiently reduces 2-keto-L-gulonic acid to L-Idonic acid [40]. Furthermore, L-idonate dehydrogenase (L-IdnDH) is confirmed to be a key enzyme in the TA biosynthetic pathway, which is involved in the tartaric acid synthesis and acts independently of the enzyme suite involved in the Smirnoff–Wheeler pathway [11,28]. The functions of L-IdnDH have been demonstrated in higher plants, but the mechanisms regulating TA need to be intensively studied.

4.1. Enzymes of the L-Galactose Pathway for AsA Biosynthesis

4.1.1. GDP-D-Mannose-3′,5′-Epimerase, GME

GME is a key enzyme in the AsA biosynthesis pathway in plants, catalyzing the conversion of GDP-D-mannose to GDP-L-galactose or GDP-L-gulose. GDP-L-gulose is considered a novel intermediate in the alternative pathway for AsA biosynthesis in plants [34,41]. The function and expression pattern of GME have been confirmed in early studies, and it is also a critical regulatory factor for AsA accumulation and cell wall biosynthesis [42]. Silencing of *GME* via RNAi in tomatoes effectively reduces the content of AsA in plants, but also affects plant growth and development [41]. Additionally, overexpression of *SlGME1* and *SlGME2* increases the total AsA content in leaves and fruits and enhances the stress tolerance of tomatoes [43]. Ma et al. (2014) isolated the *MsGME* gene, encoding a key en-

zyme in AsA biosynthesis, from alfalfa (*Medicago sativa*). Overexpression of *MsGME* in *Arabidopsis* results in increased transcript levels of GDP-D-mannose pyrophosphorylase (GMP), L-galactose-1-phosphate phosphatase (GPP), and GDP-L-galactose phosphorylase (GGP), leading to an increase in AsA content [44]. Thus, GME not only regulates the accumulation of AsA but also enhances the tolerance of transgenic plants to abiotic stress. Previous research on GME has mainly focused on model plants, and previous findings have revealed its significant regulatory role in AsA biosynthesis. Investigating the regulation of AsA and TA by GME in grapes will be a research priority.

4.1.2. GDP-L-Galactose Phosphorylase, GGP/VTC2

GDP-L-galactose phosphorylase, also named VTC2, is a locus on chromosome 4 in 3 AsA-deficient mutants of *Arabidopsis* that have been genetically mapped [45]. This enzyme is also a member of the HIT protein superfamily GalT/Apa1 branch and catalyzes the conversion of GDP-L-galactose to L-galactose-1-P [45–47]. Dowdle et al. (2007) identified two genes encoding GDP-L-galactose phosphorylase in *Arabidopsis*, namely *VTC2* (At4g26850) and *VTC5* (At5g55120). The double mutant of *VTC2* and *VTC5* could only survive when provided with exogenous AsA, indicating that the GDP-mannose pathway relies solely on GGP as the primary physiological source for AsA synthesis [48].

In 2012, Bulley conducted overexpression studies of the *GGP* gene in tomatoes, potatoes, and strawberries, and the results showed a significant increase in AsA content, highlighting the crucial role of GGP in AsA biosynthesis. However, transgenic tomato fruits with elevated AsA levels are either seedless or have nonviable seeds [49]. This may be attributed to the selective impact of GGP overexpression on the biosynthesis of cell walls in seeds by depleting GDP-mannose and its precursors [41,49]. Despite GGP being a critical rate-limiting step in the L-galactose pathway for AsA biosynthesis, our understanding of the regulatory mechanisms controlling AsA levels by this enzyme in plants remains limited. The extent to which the expression of *VTC2* and *VTC5* is co-regulated by other proteins to modulate AsA accumulation represents an intriguing unanswered question in this field.

4.1.3. L-Galactose Dehydrogenase, GalDH

GalDH is a monomeric enzyme and a member of the aldo-keto reductase (AKR) protein superfamily. GalDH catalyzes the oxidation of L-galactose to L-galactono-1,4-lactone and is considered one of the key rate-limiting enzymes in the L-galactose pathway for AsA synthesis [50]. The high content of AsA in both the peel and flesh of apples is associated with the expression levels and enzyme activity of GalDH and galactono-1,4-lactone dehydrogenase (GalLDH) [51]. Similarly, in kiwifruit, the activity of GalDH and GalLDH correlates with the accumulation trend of AsA and shows a significant positive correlation with AsA levels [52]. These findings suggest that both enzymes play a crucial role in AsA biosynthesis and jointly regulate the accumulation of AsA in fruits.

4.1.4. L-Galactono-1,4-Lactone Dehydrogenase, GalLDH

Plants, algae, and the majority of animals have the ability to synthesize AsA, but humans lack the final enzyme in the ascorbic acid synthesis pathway, L-galactono-1,4-lactone dehydrogenase (GalLDH) [34]. Therefore, humans do not have the capacity to synthesize ascorbic acid and only rely on vegetables and fruits as their primary sources of AsA. GalLDH catalyzes the conversion of L-galactono-1,4-lactone to AsA, and it is considered a key rate-limiting enzyme in the L-galactose pathway for AsA synthesis. This pathway, known as the Smirnoff–Wheeler pathway, is widely recognized as the main route for AsA accumulation in plants [30]. GalLDH, the very last crucial enzyme in the L-galactose pathway, directly influences the AsA content through its enzymatic activity and transcription levels [52]. The expression of the *GalLDH* gene is closely associated with the AsA content in grape berries, with a peak observed during the ripening stage. Research has shown that increasing *GalLDH* expression can raise the AsA levels in plants [33]. Similar findings

have been reported in apple [51], kiwifruit [52], and strawberry [53], where the activity of GalLDH and its correlation with AsA accumulation have been observed. To summarize, the expression levels of genes involved in the L-galactose pathway are directly linked to the AsA content in plants.

4.2. Enzymes of the Alternative Pathway for AsA Biosynthesis

4.2.1. L-Gulono-1,4-Lactone Oxidase, GulLO

L-gulono-1,4-lactone oxidase, an enzyme that acts at the intersection of the glucose and myoinositol pathways, catalyzes the synthesis of ascorbic acid from L-gulono-1,4-lactone (LgulL), and there is little information on the enzymes involved in this step of the reactions in plants. Previous studies have revealed the involvement of GulLO in AsA biosynthesis, where overexpression of the Arabidopsis AtGulLO homologue results in a significant increase in total AsA levels in transgenic tobacco cells under L-GulL treatment [54]. In 2017, the activity of AtGulLO5 in converting L-GulL to AsA was first demonstrated in *Arabidopsis* by Aboobucker et al. (2017), which over-expressed Arabidopsis GulLO5 did not lead to elevated foliar AsA levels after L-GulL feeding, another member of the AtGulLO family (AtGulLO3) have obtained similar results. This is most likely due to the AtGulLO5 and AtGulLO3 have a low catalytic efficiency in comparison to GalLDH. The author considered that both AtGulLO3 and AtGulLO5 are regulated post-transcriptionally by two different mechanisms, AtGulLO5 may need an effector molecule to increase its catalytic efficiency while AtGulLO3 may need to be protected from the proposed rapid turnover [55]. GulLO catalyzes the production of AsA from L-GulL is limited by the availability of the GulLO enzyme, which is related to those two different regulatory mechanisms. The function and characterization of the GulLO enzyme are currently unclear and this needs to be elucidated in future studies.

4.2.2. D-Galacturonate Reductase, GalUR

It has been demonstrated that ascorbic acid in ripe strawberry fruit can be biosynthesized via the D-galacturonic acid pathway. D-galacturonate reductase converts D-galacturonic acid to L-galacturonic acid, which is subsequently converted to L-galactose-1,4 lactone for further oxidation to AsA [35]. Meanwhile, overexpression of the *FaGalUR* gene in *Arabidopsis* [35] and tomato [56] shows an increase in AsA content, especially in light red tomato fruits. Melino et al. (2009) investigated the developmental expression of the alternative pathway for Asc biosynthesis in grapes, and it was shown that D-galacturonic acid reductase gene expression was up-regulated in ripe berries, while there was residual expression of Smirnoff–Wheeler Asc biosynthetic pathway genes and the TA biosynthetic genes [30]. In addition, the results of researchers also suggest that the D-GalUA pathway plays a role in berry colouring begins (pre-veraison), as *VvGalUR* expression is increased during ripening and the expression of the gene is strictly dependent on light [33]. It is noteworthy that the Smirnoff–Wheeler pathway supports the biosynthesis of AsA in immature berries, whereas the D-galacturonic acid pathway supports the biosynthesis of Asc in mature berries, which is both pathways converted to AsA via the activity of L-galactose-1,4 lactone dehydrogenase [57,58]. Taken together, *VvGalUR* expression correlates with berry AsA content and the D-galacturonic acid pathway is important for AsA synthesis in grapes.

4.2.3. Aldonolactonase, Alase

Aldonolactonase (Alase) is a key enzyme in the D-galacturonate pathway, which converts L-galactonate to L-galactono-1,4-lactone (L-GalLDH), a precursor of AsA [59]. In 2012, researchers fed Micro-tom with D-galacturonate (D-Gal) and found increased AsA content in red tomato fruits, but not in green fruits. Alase and GalUR enzyme activity was detected from both green and red tomato fruits in enzyme extracts, with Alase showing twice the enzyme activity in ripe red fruits compared to unripe green fruits [60]. These findings suggest that the Alase plays an important role in fruit ripening. Yao et al. (2017)

isolated three Alase family genes from kiwifruit and showed that *Alase* genes are expressed to varying degrees in different tissues of kiwifruit during growth and development, and the expression levels increase during fruit ripening [61]. This indicates that Alase family members play an important role in AsA synthesis in kiwifruit. At present, little is known about the functions of *Alase* genes in AsA synthesis and accumulation, and further understanding is needed in the future.

4.2.4. Myo-Inositol Oxygenase, MIOX

Myo-inositol oxygenase is a unique monooxygenase that catalyzes the conversion of myo-inositol (MI) to D-glucuronic acid. In 2004, researchers cloned and characterized the *MIOX* gene for the first time in *Arabidopsis*, which was identified in chromosome 4 (*miox4*) of Arabidopsis ecotype Columbia, confirmed its enzymatic activity in a bacterially expressed recombinant protein; *Miox4* overexpression increases AsA levels in *Arabidopsis* leaves by 2–3 fold, demonstrating that MIOX can increase AsA levels in plants, and MI can also act as a biosynthetic precursor of AsA in plants [36]. However, it remains controversial whether the MI pathway of AsA plays a role in plants. In 2009, Endres and Tenhaken overexpressed Miox in *Arabidopsis thaliana* and found that Miox overexpression lines had higher transcript levels and enzyme activity, but the AsA levels were not increased in these transgenic plants. The study revealed that Miox has a less significant effect on AsA biosynthesis and the higher enzyme activity only increased the efficiency of myoinosi-tol conversion to D-GlcUA, resulting in the Miox overexpression lines exhibiting a lower steady-state level of myoinositol [62]. As there is more than one pathway involved in AsA biosynthesis and the L-galactose pathway plays a dominant role, the role played by these alternative pathways is negligible, whereas, in recent MI feeding experiments, it has been shown that the inositol pathway promotes AsA biosynthesis in leaves and fruit. Moreover, overexpressed the *MIOX4* gene in tomatoes and the overexpression lines have a significant increase in total ascorbic acid content in leaves and ripe fruit [63]. However, whether MIOX is involved in AsA biosynthesis is highly controversial, but it is well established that *MIOX* overexpression plays an important role in plant resistance to abiotic stresses, as confirmed in rice (*Oryza sativa* L.) [64].

4.3. TA Biosynthetic Enzymes

4.3.1. L-Idonate Dehydrogenase, L-IdnDH

L-idonate dehydrogenase (L-IdnDH) is a crucial enzyme involved in the oxidation of L-idonic acid to 5-keto-D-gluconate, which is the rate-limiting step in the biosynthesis of TA in *Vitis* plants. Debolt et al. (2006) proposed that L-IdnDH belongs to the sorbitol family and is a characteristic enzyme associated with TA biosynthesis in higher plants. It is unable to detect the TA but hyperaccumulates AsA in *Ampelopsis aconitifolia*, due to the species *Ampelopsis aconitifolia* absent a gene encoding L-IdnDH [15]. Again, the results of Melino et al. (2009) confirmed that the biosynthesis of AsA to TA occurs in immature berries. Additionally, they observed that L-IdnDH gene expression was up-regulated in the pre-veraison stage, which was consistent with the timing of TA accumulation [30]. These findings provide further evidence supporting the conclusion that L-IdnDH is a crucial gene for TA biosynthesis. Debolt et al. (2006) believed that the reduction of 5-keto-D-gluconate to L-idonate is catalyzed by an enzyme similar to L-IdnDH in *Fusarium* sp. no. [15]. L-IdnDH contains three potential isoforms, two of which isoforms (XM_002267626.2 and NM_001280954.1) were highly expressed specifically in young berries, but a third isoform (XM_002269859.2) presented an increasing trend and reaches a high transcription level in ripe berries [65]. Wen et al. (2014) concluded that the expression of L-IdnDH was similar among different grape varieties, while the level of TA accumulation differed between grape cultivars [66]. In the case of European-type vine varieties, the accumulation of TA was positively correlated to the expression of isoforms XM_002267626.2 and NM_001280954.1. As for Chinese-type grapes, a high level of TA should be related to a slower decline in L-IdnDH protein level with berry maturity [65]. In a

subsequent study, Jia et al. reported three L-IDH isoforms in *V. vinifera*, of which *VvLIDH1* and *VvLIDH3* genes encoding L-idonate dehydrogenase categorized as "class II" plant sorbitol dehydrogenases (SDH), and *VvLIDH3* was definitively shown to oxidize L-idonate. On the other hand, the *VvLIDH2* gene categorized as a "class I" SDH, which does not catalyze the L-idonate oxidation reaction and is presumably involved in sorbitol metabolism rather than TA biosynthesis [67]. Furthermore, the characteristics of the L-IDH orthologs have been described in Burbidge's review [8]. Many transcriptional datasets indicate that *L-IdnDH* expression appears to correlate with the time of TA synthesis. However, high levels of *L-IdnDH* expression are not observed in high TA grape varieties, which is consistent with Cholet's research results; they believed that L-IdnDH may not be the only key enzyme in the TA biosynthesis pathway [11,66].

4.3.2. 2-Keto-L-Gulonate Reductase, 2-KGR

In a pioneering radioisotope tracing study, Saito et al. (1982) infused ^{14}C into all AsA metabolites in grape slices. Their findings revealed that ^{14}C initially appeared in three metabolites, namely L-idonic acid, L-idono-y-lactone, and 2-keto-L-gulonic acid, after incorporation of ^{14}C into TA [68], indicating that at least one of these three compounds acts as an effective precursor of TA and lies in the metabolic pathway between AsA and TA. Previous studies have shown that 2-keto-L-gulonate reductase (2-KGR) catalyzes the reduction of 2-keto-L-gulonic acid (2-KGA) to L-idonic acid [69]. Burbidge (2011) identified three potential 2-keto-D-gluconate reductases (TC61548, TC59682, and TC55752) by comparing the genome of *V. vinifera* with enzymes that catalyze similar reactions in bacteria. Among the three candidate genes, the expression pattern of TC59682 strongly coincided with the biosynthesis of TA, which was annotated as a 2-keto-L-gulonate reductase. However, Expression patterns of TC61548 and TC55752 suggest they are not involved in TA biosynthesis [70]. This suggests that 2-keto-L-gulonate reductase plays an important role in the TA biosynthesis pathway. Jia et al. (2019) have recently characterized the enzymatic activity of 2-keto-L-gulonic acid reductase (Vv2KGR) from grapes, which belongs to the D-isomer-specific 2-hydroxyaid dehydrogenase superfamily with the highest similarity to hydroxypyruvate reductase isoform 2 in *Arabidopsis thaliana*. Moreover, the transcriptional profile of Vv2KGR has been found to be consistent with the accumulation of TA during grape fruit development, suggesting a crucial role of 2-KGR in TA biosynthesis [40]. This enzyme has been identified in several bacteria, including *Erwinia herbicola* [71], *Brevibacterium ketosoreductum* [69], *Escherichia coli* [72], and acetic acid bacteria, but rarely reported in plants.

4.3.3. Transketolase (TK) and Tartaric Semialdehyde Dehydrogenase (TSAD)

The involvement of transketolase (TK) and tartaric acid semialdehyde dehydrogenase (TSAD) in grapevine TA synthesis has yet to be confirmed. However, 5-keto-D-gluconate (5-KGA) is widely acknowledged as a constituent of the grapevine TA biosynthetic pathway, although the enzyme catalyzing its conversion remains unidentified. Saito et al. (1984) discovered 5-KGA as a metabolite of AsA in immature grape slices [73]. Gluconate 5-dehydrogenase (GA 5-DH), a pyroquinoline quinone (PQQ)-dependent membrane-bound dehydrogenase, is present in Gluconobacter suboxydans, which oxidizes gluconate oxidation to 5-KGA; thus, the researchers proposed that a ketolase such as transketolase or phosphoketolase could remove the ketol moiety of 5-KGA to form tartaric acid semialdehyde, which could be further oxidized by TSAD to generate TA [74].

The researchers identified a candidate gene for *TSAD* encoding a homolog of succinic acid semialdehyde dehydrogenase in plants, which has the potential to oxidize tartaric acid semialdehyde to TA [15]. Wang et al. (2022) molecularly modified the transketolase in *E. coli* (K12 strain) and obtained the mutant enzyme TKTA-M, which catalyzes the formation of tartaric acid semialdehyde from 5-KGA [75]. Prior studies have provisionally verified the possibility of TA synthesis from 5-KGA in the presence of TK and TSAD, but

the characteristics and roles of the TK and TSAD associated with tartaric acid synthesis require further investigation and validation.

5. Metabolism of TA

TA is not metabolized by grape berry cells via respiration in the same manner as malic acid, and the level of TA in the grapes remains relatively consistent throughout the ripening process [76]. Endogenous TA in grapevine berries is not broken down at a significant rate, whereas degradation of exogenously applied radiolabeled TA could be recovered as CO_2 from excised grape berries [8,77]. The TA formed is essentially metabolically inert [30]. The biosynthetic and metabolic pathways of MA and TA are distinctly different. MA is released from vacuoles during grape ripening and metabolized through glyconeogenesis, respiration, and secondary metabolism, whereas TA is formed by the catabolism of AsA [23].

Ruffner et al. (1983) suggested detecting a decrease in TA concentration post-veraison, which is attributed to a dilution, not a dissimulation [78]. Our data showed similar results (data not published), TA is calculated on a per berry basis, the concentration of TA remains relatively constant during ripening, and calculation of TA on grams shows an overall decrease in the amount of TA in post-veraison. L-(+)-Tartaric acid-l,4-^{14}C was fed to grape berries via the peduncle by Saito et al. (1968), and the result showed that a part of the L-(+)-tartaric acid was metabolized in grape berries, most of it was retained in the berry as a salt form, and some of the tartrate was converted back to free TA at the last stage of the ripening process (82–100 days after flowering) [79]. The above demonstrates the hypothesis that the TA content tends to reach a steady state during the ripening process, due to the equilibrium between the synthesis and decomposition of tartaric acid. The question of whether the decrease in TA levels during post-veraison is attributable to dilution or catabolism is debatable, and perhaps both phenomena are at play. Furthermore, it has been reported that microorganisms can decompose TA. For instance, the catabolism of TA by *Botrytis cinerea* produced ten organic acids (L-malic, pyruvic, acetic, oxalic, oxaloacetic, L-lactic, a-ketoglutaric, D-glyceric, succinic, and citric acids). The characteristic action of *B. cinerea* in reducing the level of L-tartaric acid may be an effective way of improving the tartrate stability of wines [80]. In addition, it has been found that bacteria [81] and fungi [82] have the capacity to oxidize or dehydrate all of the three optical isomers of tartaric acid, leading to oxaloacetic acid [83], glyoxylic acid [84], and glyceric acid [85]. These microorganisms are able to metabolize TA as a carbon source. Crouzet and Otten (1995) reported the presence of four intact open reading frames in the Agrobacterium vitis genome encoding enzymes capable of degrading TA [86]. However, no enzymatic studies on TA metabolism have been performed in higher plants.

6. Factors Affecting TA Content

The variation in TA content can be observed among different grape varieties and also among different parts and tissues of the grape fruit. In addition, external conditions such as light exposure and the use of plant growth regulators can impact the biosynthesis of TA.

6.1. Environmental Factors

Environmental factors such as light and temperature have been shown to affect acid content in grapes, such as high temperatures reducing organic acid concentrations. While MA is most significantly affected by temperature and light, TA concentration is not affected by temperature in ripe grape berries [87].

Kliewer et al. (1976) reported that the application of artificial shade delayed the maturation of grape berries. Additionally, the study revealed that MA concentrations in ripening berries grown in 30% sun were 13% higher than those grown in full sun, but the TA concentrations were almost identical in berries grown in 21% and 30% sun [88]. The loss of MA and TA whether the grapes were grown in high temperature or high light conditions. The rate of loss was very rapid at the early stages of berry ripening and then leveled off, but MA always declined faster than TA [89]. DeBolt et al. (2008) used three levels

of light (highly exposed, moderately exposed, and light-excluding boxes) to determine the TA content of individual berries throughout development and showed that light exclusion treatments significantly reduced berry weight and TA accumulation at all stages of development [90].

Kliewer employed $C^{14}O_2$ to track the incorporation of carbon into organic acids in berries cultivated at different temperatures. The results indicated that the content of C^{14} incorporated into organic acids in nearly ripe berries was higher at low temperatures [91]. The temperature had no significant effect on the content of TA in nearly ripe berries, whereas the content of TA in green berries was higher at 20 to 25 °C than at the higher temperatures. It has been demonstrated that light regulation of AsA biosynthesis can significantly impact the accumulation of TA in grape berries. Specifically, transcription of the AsA biosynthesis gene *VvLGalDH* and the upstream genes *VvVTC2* and *VvGME* is independent of light, while light-mediated regulation of AsA biosynthesis during grape fruit development acts mainly via *VvGalLDH* [92].

Further research has demonstrated that treatment with NAA delays ripening and significantly inhibits anthocyanin accumulation while increasing tartaric acid content in grape berries [93]. Conversely, treatment of grape inflorescences and clusters with 6-BA (6-benzyladenine) at day 5 before flowering, day 3 after flowering, and day 10 after flowering reduces TA content in ripe fruits, which is attributed to the inhibition of the expression of *L-IdnDH*, the key enzyme gene for the biosynthesis of tartaric acid, so the synthesis of tartaric acid is affected [94]. Salicylic acid treatment during the flowering period also results in concentration-dependent effects on TA content in grape berries, with 3 mmol/L salicylic acid treatment reducing TA by 15.05% at day 60 after flowering, and 5 mmol/L salicylic acid treatment increasing TA by 17.07% at day 80 after flowering [95].

These findings suggest that environmental factors play an important role in regulating TA synthesis in grape berries through their effects on the expression of relevant genes in the biosynthesis pathway. Clarifying the mechanism of TA synthesis regulation is crucial for the selection and breeding of high-acid varieties of wine grapes.

6.2. Grape Training Systems and Rootstocks

Research has shown that training systems and rootstocks have a certain impact on the content of sugar and organic acid in fruits. Compared with training systems of Single Guyot, Vertical Shoot-positioned, and Four-arm Kniffin can significantly improve the yield of 'Cabernet Sauvignon' grapes, and the content of TA in fruit is significantly higher than that of the other training systems [96]. Also, Niu (2019) reported that the content of TA in berries is slightly higher in the fan-shaped tree shape than in the "厂"-shaped tree shape (the grapevine is shaped to resemble the Chinese character for "厂"), self-rooted trees are significantly higher than that of grafted trees (using SO4 rootstocks) after 25 days of flowering, and there is no difference in other stages [97]. The rootstocks have a significant impact on the content of TA and MA in berries. For example, the TA content in 'Malbec' berries exceeds that of 'Négrette', and when these two varieties were grafted onto 3309c rootstocks showed higher TA content compared to self-rooted plants [98]. Also, grafting 'Yinhong' on 'SO4' and 'Beta' rootstocks, compared with self-rooted seedlings, could improve the chlorophyll content, soluble solids, total sugar, AsA content, fruit solid acid ratio, and yield of 'Yinhong' grapevine [99].

The quality of grape fruits varies depending on the training system and rootstock used. The use of specific rootstocks significantly increases grape yield and fruit quality compared to self-rooted plants. By studying and comparing the effects of different tree training systems and rootstocks on the organic acid composition of wine grapes, valuable theoretical guidance can be provided for enhancing the quality of grapes and wine.

6.3. Regulatory Effects of Transcription Factors

Transcription factors play a vital role in regulating the biosynthesis of plant metabolites by binding to the promoter sequences of key enzyme genes. Their regulatory role is

characterized as 'multi-point regulation' and they have a higher regulatory status than the key enzymes in biosynthesis [100]. Studies have revealed that bHLH, WRKY, AP2/ERF, and MYB, among others, are the main transcription factor families involved in organic acid biosynthesis [101–104]. However, the regulatory roles of transcription factors of the same family are not entirely consistent. Transcription factors can regulate gene transcription independently or form complexes with other transcription factors to co-regulate plant metabolic activities [105,106].

It has been shown that the *SlbHLH59* transcription factor promotes ascorbic acid accumulation in tomato fruit by directly binding to the promoters of the PMM, GMP2, and GMP3 genes in the D-mannose/L-galactose synthesis pathway, which is one of the ascorbic acid biosynthetic pathways [107]. In addition, *ZmbHLH55* (helix-loop-helix 55) transcription factor has also been shown to regulate AsA biosynthesis in maize, positively regulating the expression of *ZmPGI2*, *ZmGME1*, and *ZmGLDH*, but negatively regulating the expression of *ZmGMP1* and *ZmGGP*, and overexpression of *ZmbHLH55* enhances salt tolerance in plants [108]. These findings indicate that *bHLH* transcription factors can act as activators or repressors to regulate the expression of structural genes in AsA biosynthesis.

A study reported that overexpression of *SlICE1* in tomatoes enhances the accumulation of antioxidants (e.g., β-carotene, lycopene, and ascorbic acid) and regulates antioxidant activity by accumulating multiple antioxidants [109]. Meanwhile, the brassinosteroid (BR) response transcription factor Brassinazole resistant 1 (BZR1) reported has a similar function [110]. *Arabidopsis* KONJAC1 and KONJAC2 (KJC1 and KJC2) are shown to be involved in GDP-Man synthesis, thereby affecting AsA accumulation through the stimulation of VTC1 GMP activity, whereas KJC themselves do not or rarely synthesize GDP-Man [111]. Another HD-Zip I family transcription factor, SlHZ24, promotes the accumulation of AsA in tomatoes, and regulates AsA biosynthesis through multiple targets by interacting with *SlGME2* and *SlGGP* promoters, and overexpression of *SlHZ24* significantly enhances AsA levels and oxidative stress tolerance via regulation of AsA biosynthetic genes [112].

In addition, researchers have identified a gene encoding an ethylene response factor (ERF) in Arabidopsis (*AtERF98*) [113]. The knockout and knockdown mutants of Arabidopsis *AtERF98* decrease AsA levels, but overexpression of *AtERF98* increases AsA levels. *AtERF98* modulates AsA biosynthesis by binding to the promoter of *VTC1* directly and regulating the expression of AsA synthesis genes [101]. A new transcription factor, BcERF070, has also been identified in Chinese cabbage, where up-regulation of *BcERF070* results in increased AsA content and down-regulation of *BcERF070* results in decreased AsA content, and this transcription factor affects the accumulation of AsA by regulating genes involved in AsA biosynthesis and metabolic pathways [114]. Furthermore, Chen et al. demonstrated through a dual-luciferase reporter and yeast one-hybrid assays that *AcERF91* in kiwifruit is able to bind to and directly activate the activity of the promoter of the gene encoding GDP-galactose phosphorylase (*AcGGP3*), and that transient expression of *AcERF91* in kiwifruit fruit results in a significant increase in AsA content and *AcGGP3* transcript levels, indicating that *AcERF91* is regulating the accumulation of AsA [115]. We therefore supposed that ERF transcription factors are also involved in regulating AsA biosynthesis in grapes, regulating the upstream stages of grape TA biosynthesis via the D-mannose/L-galactose (D-Man/L-Gal) pathway. Recently, Lu et al. (2022) reported potential transcription factors for AsA biosynthesis in date palm, of which *ZjERF17* (*LOC107404975*), *ZjbZIP9* (*LOC107406320*), and *ZjGBF4* (*LOC107421670*) are most likely to be important genes regulating AsA synthesis [116]. A gene encoding a 1R-subtype myeloblastosis (MYB) protein, *AceMYBS1*, is found to bind to the *AceGGP3* promoter in *Actinidia eriantha* and promote AsA accumulation. The bZIP transcription factor *AceGBF3* (G-box binding factor) also increases AsA content and interacts with *AceMYBS1* to jointly promote AsA synthesis and *AceGGP3* expression [117].

These transcription factors positively regulate the accumulation of AsA, but transcription factors that negatively regulate the accumulation of AsA are also present (Figure 2).

For example, researchers have isolated the *AMR1* gene (for ascorbic acid mannose pathway regulator 1) from an activation-tagged (AT) Arabidopsis mutant that is inversely correlated with changes in leaf AsA content and appears to play an important role in modulating AsA levels in *Arabidopsis* by regulating the expression of major pathway genes in response to developmental and environmental cues [118]. The photomorphogenic factor COP9 signalosome subunit 5B (CSN5B) in *Arabidopsis* interacts with VTC1 to negatively regulate AsA biosynthesis, and thus regulate the plant response to oxidative and salt stresses [119]. In another report, L1L4 (or NF-YB6), encoding a heterotrimeric nuclear transcription factor, an established repressor of AsA biosynthesis, also negatively regulates AsA accumulation [120,121]. In tomatoes, transcription factor *SlNFYA10* can bind to the promoter of *SlGME1* and negatively regulate AsA biosynthesis by hindering the expression of *GME1* and *GGP1* in tomato fruit. It is the first transcription factor identified so far that negatively regulates the AsA biosynthetic pathway at multiple loci [122]. Abscisic acid (ABA) INSENSITIVE 4 (ABI4) acts as a pivotal transcription factor downstream of the ABA signaling pathway; in *Arabidopsis*, ABI4 binds directly to the promoter of the *VTC2* (*VITAMIN DEFECTIVE 2*) gene and inhabits *VTC2* transcription and AsA biosynthesis [123,124].

As an essential synthetic precursor of TA, AsA is presumed to play a crucial role in the biosynthesis of TA. Therefore, the transcription factors involved in regulating the synthesis of AsA in the upstream stage of TA may directly or indirectly affect the accumulation of TA in the downstream stages. However, the specific regulatory mechanisms require further investigation. Although the metabolites and regulatory mechanisms of AsA in grapes have not been fully elucidated, previous research has provided us with adequate theoretical support and a new research direction for the transcriptional regulation of TA.

7. Future Perspectives

In spite of the extensive investigation of TA, the complete biosynthetic pathway of grapevine TA remains unresolved. Although previous studies have reported some key enzymes in the biosynthetic pathway of TA, the functions and regulatory mechanisms of these enzymes are yet to be confirmed. This paper presents a review of the progress in previous research on TA in grapes, and delves deeply into the significant roles of TA in grapes, including its structural properties, distribution characteristics, biosynthesis, catabolism, and transcriptional regulation, as these interrelationships are closely linked to the enhancement of TA content.

With the increasing global warming trend, the susceptibility of organic acids to climate change, which in turn determines the fruit quality of grapes, becomes a significant challenge for the wine industry. The accumulation of TA is also influenced by light and temperature, posing a significant test for the industry. Artificial control of light and temperature and the addition of large amounts of TA in the winemaking process are not only challenging to implement but also increase production costs and fail to meet market demand for wine. At the same time, exploring the expression of organic acid biosynthesis-related genes in cultivation techniques can also provide a theoretical basis for improving fruit quality by regulating TA synthesis and metabolism in grape fruits in the future, such as selecting suitable rootstocks and tree shapes suitable for wine grape varieties.

Although traditional breeding for improving the TA characteristics of grapes is time-consuming and challenging, recent advances in genetic engineering techniques have been employed to enhance plant breeding, including genetic modification of plants through recombinant DNA technology without changing varietal characteristics to acquire the desired agronomic traits for production. In addition, the rapidly developing transcriptomics approach is now widely used in grapevine and has become a powerful tool for molecular biology research in grapevine. The transcriptional sequences and expression profiles of the genes involved in the biosynthesis of AsA and TA can be revealed by grape transcriptome analysis to understand the structural features and molecular functions of these enzymes in grapes, which can provide a strategy for designing and improving the kinetic properties of the target enzymes. Important differential metabolites or important pathways were ob-

tained by metabolome analysis. The combined transcriptome data identified target genes altered in TA key metabolic pathways, providing a theoretical basis for further mining of key gene functions to elucidate the transcriptional regulatory mechanisms of TA. Although extensive research has been conducted on the biosynthesis and regulatory mechanisms of AsA, the precise mechanisms underlying TA accumulation in plants remain unclear. Overexpressing genes associated with the Smirnoff–Wheeler pathway offers a potential strategy to increase AsA levels and subsequently the downstream TA content. Therefore, AsA, as a precursor in TA synthesis, plays an important role in this process. Clarifying the functions of key enzyme genes in the AsA metabolic pathway and TA synthesis pathway, exploring the mechanisms by which transcription factors regulate their expression, and regulating TA biosynthesis at the molecular level requires further exploration in future studies.

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