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# Key-enzymes involved in the biosynthesis of resveratrol-based stilbenes in *Vitis* spp.: a review

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**Abstract** Polyphenols are a large class of plant specialized metabolites with interesting biological properties. Among them, the stilbene phytoalexins are particularly abundant in grapevine gaining considerable applications in the cosmetic and nutraceutical industry. The well-studied stilbene biosynthetic pathway uses phenylalanine to generate resveratrol, the primary stilbene core synthesized in grapevine. A set of enzymes further metabolize resveratrol producing a diversity of stilbenes with different properties, activities and stabilities. In grapevine, 13 enzymes have been identified with the ability to use resveratrol as a substrate, including ten peroxidases, two glycosyltransferases and one *O*-methyltransferase. Peroxidases and methyltransferases are the most studied enzymes in grapevine, especially under stress conditions while the role of plant laccases and hydroxylases in stilbene metabolism is still poorly described. This article provides an overview of the key enzymes involved in the synthesis of resveratrol-based derivatives in *Vitis* spp. Perspectives to identify new enzymes are discussed, which could be further used for stilbene bioproduction using biotechnologies.

**Keywords** Stilbenes · Resveratrol · Resveratrol derivatives · Decorating enzymes · Peroxidases

## Abbreviations

HRP	Horseradish peroxidase
MeJA	Methyl jasmonate
CD	Cyclodextrins
GT	Glycosyltransferase
UGT	UDP-glycosyltransferase
STS	Stilbene synthase
ROMT	Resveratrol <i>O</i> -methyltransferase
OMT	<i>O</i> -methyltransferase
TF	Transcription factor

## Introduction

Plant secondary (or specialized) metabolites are molecules derived from the primary metabolism involved in a broad range of physiological processes, but not in plant growth and development. This concept was first defined by Kossel (1891). Secondary metabolites are distinguished from primary metabolites by their structure, function, and distribution in plants (Jan et al. 2021), and are defined by their important role in plant environment adaptation, especially in plant defense and signaling (Bourgaud et al. 2001). Precursors of secondary metabolites are mainly produced in major pathways of the primary metabolism: the Krebs cycle, glycolysis and pentose phosphate pathway (Jeandet et al. 2018; Jan et al. 2021). Secondary metabolites have interesting biological properties which make them attractive for the pharmaceutical and cosmetic industries (Bourgaud et al. 2001).

Plant secondary metabolites can be classified into three major categories: terpenes, phenolic compounds, and nitrogen-containing secondary metabolites (Fig. 1). The highly diverse class of polyphenols is represented by

different families and includes stilbenes (Fig. 1) (Ferrazzano et al. 2011). Figure 1 illustrates the different specialized metabolites encountered in plants and highlights the positioning of stilbenes.

Each class of phenolic compounds is represented by a wide diversity of molecules. For example, over 9,000 flavonoids have been identified (Yonekura-Sakakibara et al. 2019). This diversity is explained by the complexity of the biosynthesis pathways generating these compounds. Indeed, for most polyphenol classes, this structural polymorphism arises from variable conversion pathways of a basic molecular structure through a set of enzymes including glycosyltransferases, methyltransferases, peroxidases, prenyltransferases, hydroxylases or laccases (Jan et al. 2021). For the stilbene family, the starting building block is resveratrol (Fig. 2), and though its biosynthesis pathway is well known, most enzymes (peroxidases and the so-called decorating enzymes) that synthesize the resveratrol derivatives remain to be identified. The knowledge gap on the biosynthesis of these derivatives limits the possibilities of acting on their regulation pathways and restricts their production potential for industrial purposes.

In this review, we are focusing on the key enzymes involved in stilbene derivatives' biosynthetic pathways in grapevine. There are excellent reviews dedicating to the biological activity of stilbenes (Akinwumi et al. 2018), regulation of their biosynthetic pathways (Dubrovina and Kiselev 2017), stilbene occurrence in plants and Vitaceae (Riviere et al. 2012), stilbene bioproduction (Donnez et al. 2009; Jeandet et al. 2020), or metabolic engineering of stilbene biosynthesis pathways (Jeandet et al. 2018; Thapa et al. 2019), but to our knowledge, there are no reviews reporting on the enzymes which operate on the resveratrol skeleton to form derivatives in grapevine. Increasing knowledge on these enzymes is essential to improve our understanding of grapevine defense mechanisms and to develop biotechnological engineering methods for stilbene bioproduction. Therefore, we present and discuss advances in the identification and regulation of the key enzymes involved in resveratrol oligomerization, glycosylation, methylation, and hydroxylation in *Vitis* spp.

## Relevant significance of resveratrol and its derivatives

*Trans*-resveratrol (3,4',5-trihydroxy-*trans*-stilbene) is a phenolic compound of the stilbene family naturally produced by at least 72 plants (Valletta et al. 2021) such as grapevine (Langcake and Pryce 1976), strawberry (Sebastian et al. 2017), peanut (Sanders et al. 2000) or Japanese knotweed (Peng et al. 2013). It was first discovered in *Veratrum album* (Takaoka 1939). Resveratrol is obtained through the phenylpropanoid pathway in the same way as many specialized plant metabolites, namely flavonoids, coumarins, anthocyanins or lignins (Vogt 2010). Stilbene biosynthesis in grapevine starts with the synthesis of the stilbene building block, resveratrol (Fig. 2) (Chong et al. 2009; Jeandet et al. 2010, 2021b; Keylor et al. 2015). Then, different enzymes intervene in the conversion of resveratrol into various stilbene derivatives (Fig. 2) with different properties, activities, and stabilities compared to resveratrol (Dubrovina and Kiselev 2017). The addition of different chemical groups to the stilbene skeleton or resveratrol oligomerization by various enzymes contribute to the structural diversity of stilbenes. In grapevine and other stilbene-producing plants, these compounds are mainly synthesized after pathogen infection and act as phytoalexins (Jeandet et al. 2010).

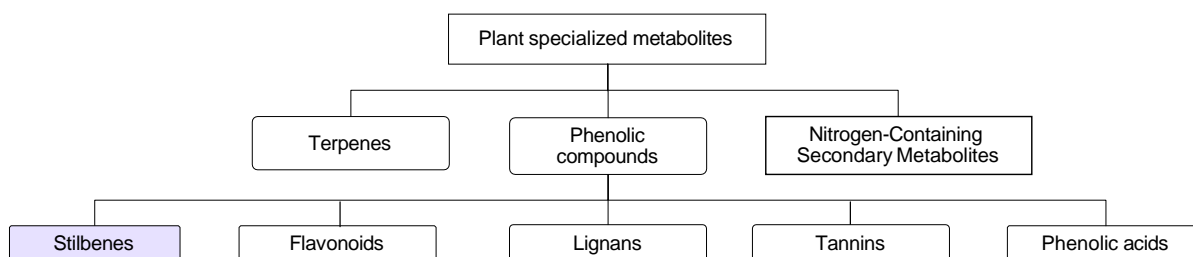


Fig. 1 Diversity of plant specialized metabolites family and positioning of stilbenes

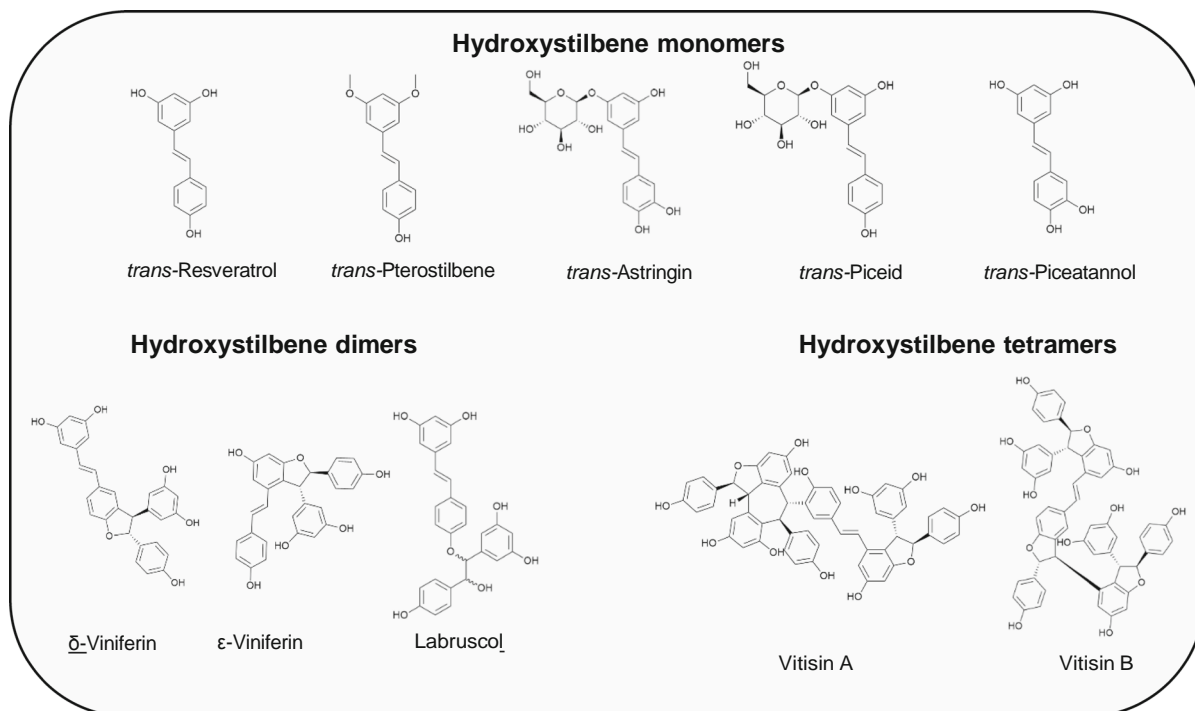


Fig. 2 Diversity of stilbene structures and main derivatives of the resveratrol core identified in *Vitis* spp.. The figure depicts the structure of hydroxystilbene monomers (*trans*-resveratrol, *trans*-pterostilbene, *trans*-astringin, *trans*-piceid and *trans*-piceatannol), stilbene dimers (d-viniferin, e-viniferin and labruscol) and stilbene tetramers (vitisin A and vitisin B)

Indeed, resveratrol derivatives are produced as defensive compounds in response to biotic or abiotic stresses in grapevine (Langcake and Pryce 1976; Jeandet et al. 2010; Hatmi et al. 2015; Aziz et al. 2016). The major compounds synthesized following exposition to UV radiation (Langcake and Pryce 1977a), water deficit (Hatmi et al. 2015) or infection by *Plasmopara viticola* and *Botrytis cinerea* (Langcake 1981; Flamini et al. 2016) are the resveratrol dimer e-viniferin (Fig. 2) and the resveratrol trimer a-viniferin. d-viniferin (Fig. 2), another resveratrol dimer was characterized later as a resveratrol metabolite produced by the laccase of *B. cinerea* (Breuil et al. 1998) and then characterized as a phytoalexin in *P. viticola*-infected grapevine leaves (Pezet et al. 2003) or in grapevine leaves and berries after treatment with beneficial bacteria inducing resistance to *B. cinerea* (Aziz et al. 2016) and *P. viticola* (Lakkis et al. 2019). Labruscol (Fig. 2), a new resveratrol dimer, was characterized in *Vitis labrusca* Concord grapevine cell culture elicited with methyl jasmonate (MeJA) and cyclodextrins (CDs) (Nivelle et al. 2017a). Resveratrol tetramers (vitisin A and vitisin B) (Fig. 2) were also identified after exposition to *Botryosphaeria dieback* (Spagnolo et al. 2014) or in elicited grapevine hairy roots (Tisserant et al. 2016). The presence of monomeric stilbenes has been reported in *Vitis vinifera* leaves such as pterostilbene (Fig. 2), a methylated resveratrol (Langcake et al. 1979; Langcake 1981), exerting a higher fungitoxic activity towards *B. cinerea* compared to resveratrol (Pezet and Pont 1990). Piceatannol (Fig. 2), a hydroxylated resveratrol was detected in grape berries following *Aspergillus ochraceus* infection (Bavaresco et al. 2003). Piceid and astringin (Fig. 2), glycosylated resveratrol derivatives are produced by grapevine cell cultures after exposure to abiotic stress (Waffo Teguo et al. 1996a, b, 1998), but as in many plants defense mechanism, glycosylated derivatives have been described as non-toxic forms ensuring storage, transport and protection of those compounds from degradation (Zhang et al. 2022). Although resveratrol derivatives play an important role in grapevine defense mechanisms, the genetic diversity of stilbenes metabolism may vary among the different *Vitis* species (Duan et al. 2015; Guerrero et al. 2020) and influence their resistance to diseases (Dubrovina and Kiselev 2017).

Resveratrol derivatives are of additional interest for their biological properties, especially the *trans*-isomers, which displayed stronger bioactivity compared to the *cis*-isomers (Mikulski and Molski 2010). For instance, resveratrol exhibits neuroprotective effects in Alzheimer and Parkinson diseases by acting on different

mechanisms involved in these diseases (Arbo et al. 2020) such as protection of the dopaminergic neurons (Zhang et al. 2010). Resveratrol also has anti- cancer and chemopreventive activities (Jang et al. 1997) as well as anti-inflammatory (De Sa´ Coutinho et al. 2018), antioxidative (Krutmann and Mcdaniel 2013), and melanogenesis inhibiting properties (Satooka and Kubo 2012). Despite its well-known and pleiotropic effects, resveratrol applications are limited by its low bioavailability (Francioso et al. 2014) which could be related to limited stability and solubility (Zupancˇicˇ et al. 2015) as well as its sensitivity to light (Vian et al. 2005). Due to the low bioavailability of resveratrol and its difficulty in being formulated into drugs (Robertson et al. 2022), studies regarding the biological properties of resveratrol derivatives have increased in recent years (Li et al. 2016). Resveratrol dimers and even oligomers of higher molecular weight possess bioactivities superior to those of the monomers (Jeandet et al. 2023). For example, e-viniferin and d-viniferin were found to have anti-tumoral (Giovannelli et al. 2014), anti- inflammatory (Chung et al. 2003) and neuroprotective properties (Org et al. 2020). The dimer labruscol has shown an activity against human melanoma cells in vitro (Nivelle et al. 2017b). Moreover, e-viniferin is very effective against atherosclerosis (Zghonda et al. 2011) or in the protection of vascular endothelial cells and the heart (Zghonda et al. 2012) compared to resveratrol. The resveratrol tetramers vitisin A and vitisin B also exhibit neuroprotective activities (Chen et al. 2022). Piceid has anti-inflammatory properties (Lanzilli et al. 2012) and inhibits platelet aggregation (Orsini et al. 1997), while pterostilbene displays higher anti-inflammatory activity than resveratrol (Chong et al. 2021). Piceatannol has sparked great interest due the presence of an additional phenolic moiety on the resveratrol scaffold which may increase antioxidant activity (Saiko et al. 2008), pharmacolog- ical activity (Latruffe and Vervandier-Fasseur 2018) and bioavailability compared to resveratrol (Setoguchi et al. 2014).

## Biosynthetic pathways of resveratrol and its derivatives

The biosynthesis of stilbenes in grapevine begins with the oxidative deamination of *L*-phenylalanine to cin- namic acid by the phenylalanine ammonia lyase (PAL; EC 4.3.1.24) (Fig. 3). Interestingly, in some plants such as Poaceae, Fabales, Malvales, Asterales, Caryophyllales, Ferns and Solanales, stilbene biosyn- thesis can start from tyrosine by directly forming *p*- coumaric acid, since such plants possess a bifunctional phenylalanine/tyrosine ammonia-lyase (PTAL, EC 4.3.1.25) that can accept both substrates (Barros and Dixon 2020). Cinnamic acid is hydroxylated by cinnamate 4-hydroxylase (C4H; EC 1.14.14.91) to form *p*-coumaric acid. Then, the *para*-coumarate CoA ligase (4CL; EC 6.2.1.12) binds a CoA molecule to *p*- coumaric acid to form coumaroyl-CoA (Ferrer et al. 2008) (Fig. 3). At this step, coumaroyl-CoA is con- densed with three malonyl-CoA by the stilbene syn- thase (STS) to form resveratrol, or by the chalcone synthase (CHS) to form a chalcone, the precursor of flavonoids (Noel et al. 2005). In grapevine, the resveratrol skeleton can undergo different modifica- tions mainly catalyzed by decorating enzymes (glyco- syltransferases, methyltransferases, and hydroxylases) along with peroxidases, resulting in various resveratrol derivatives (Fig. 3). Among resveratrol derivatives, oligomers are the most diverse group (Goufo et al. 2020; Keylor et al. 2015; Jeandet et al. 2021a, b), raising questions about their formation by peroxidases.

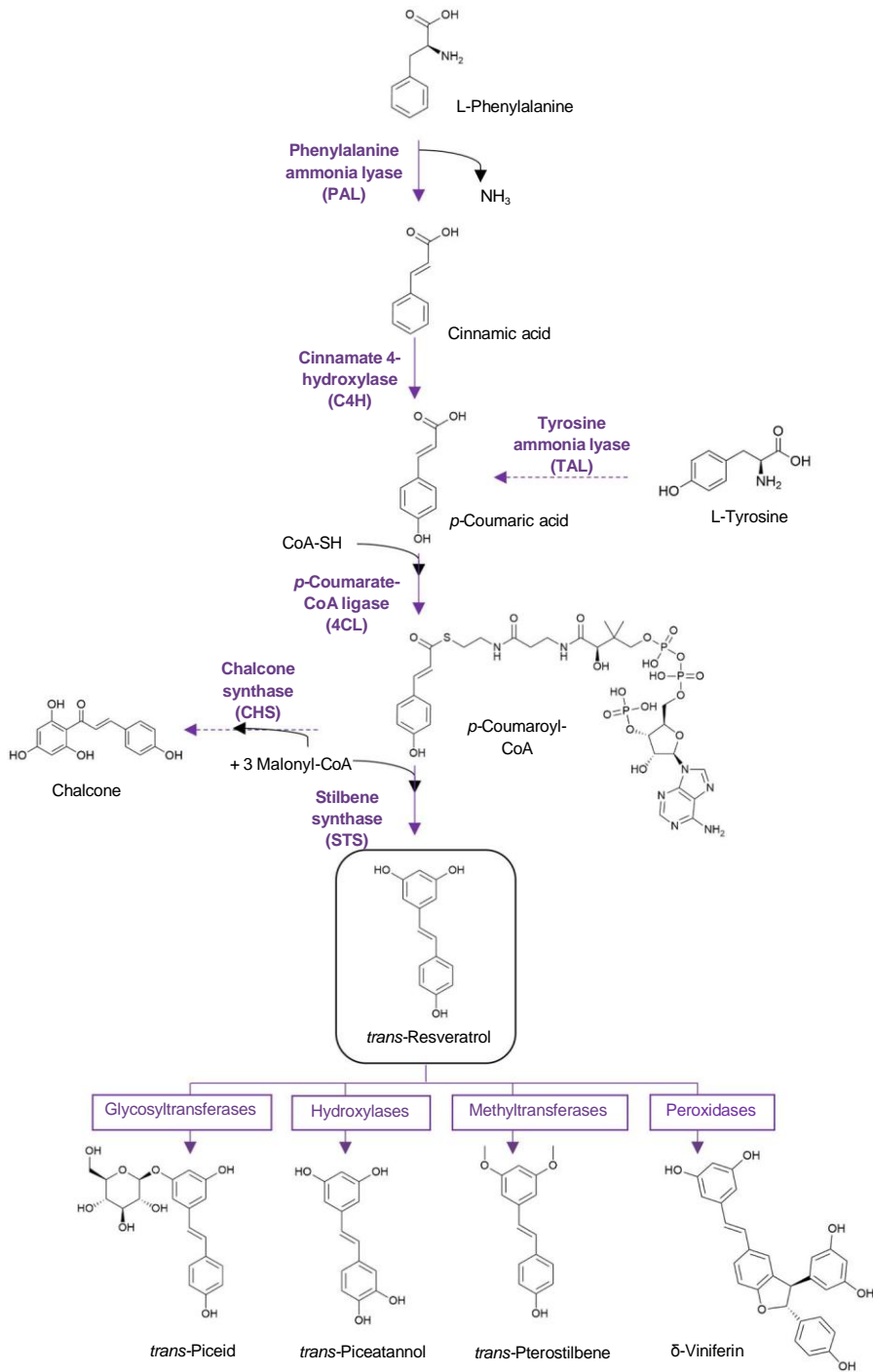


Fig. 3 Resveratrol biosynthetic pathway in grapevine and examples of the biosynthesis of some resveratrol derivatives. Resveratrol is synthesized through the phenylpropanoid pathway, involving key enzymes such as phenylalanine/tyrosine ammonia lyase (PAL/TAL), cinnamate 4-hydroxylase (C4H), 4coumarate-CoA ligase (4CL) and stilbene synthase (STS). The *trans*-piceid, *trans*-piceatannol, *trans*-pterostilbene and resveratrol oligomers such as d-viniferin can be obtained by reactions catalyzed by plant glycosyltransferases, hydroxylases, methyltransferases and peroxidases, respectively

## Peroxidases and resveratrol oligomerization

Peroxidases constitute a superfamily of enzymes found in animals, plants, and microorganisms. They catalyze redox reactions between hydrogen peroxide and a substrate (reductant) and show limited specificity towards their substrates (Hiraga et al. 2001). Plant peroxidases are divided into three classes according to their primary structure. The class III plant peroxidases (POX, EC 1.11.1.7) belong to the secretory plant peroxidases (Welinder 1992), as they are generally secreted into the cell wall, the apoplast or the vacuole (Matsui et al. 2003). They can use various substrates as electron donors such as secondary metabolites including phenolic compounds, lignins, and auxins (Hiraga et al. 2001). They are involved in the lignification process of cell walls (Ros Barcelo 1995) and lignin biosynthesis (Whetten et al. 1998) but also in defense activities. Peroxidases belong to the PR-9 family of Pathogenesis-Related (PR) proteins, which are produced in response to various biotic and abiotic stresses (Van Loon et al. 1994).

Resveratrol oligomers can be obtained by oxidative dimerization catalyzed by plant peroxidases (Langcake and Pryce 1977b; Calderon et al. 1990). Langcake and Pryce (1977b) were the first to demonstrate the oxidative dimerization of resveratrol into d-viniferin by a class III plant peroxidase, the horseradish peroxidase (HRP). HRP was used in vitro to produce different resveratrol dimers i.e. d-viniferin, pallidol, leachianol F (Wilkens et al. 2010; Li et al. 2012) and leachianol G (Zhang et al. 2017) as well as trimers such as laetevirensols A-E (He et al. 2008) and tetramers (hopeaphanol, vitisin B and vitisin C) (Takaya et al. 2002; for a review see Jeandet et al. 2023).

PR proteins and stilbenes are well characterized in grapevine as part of the defense mechanisms of grapevine during plant–microbe interactions or in response to stress. Resveratrol oligomers such as viniferins were also found to be produced after biotic or abiotic stresses (Langcake and Pryce 1977a; Langcake 1981). Efforts were made to decipher the mechanisms involved in the biosynthesis of viniferins in grapevine tissues where a correlation between the expression of a peroxidase (isoperoxidase A1) and e-viniferin biosynthesis has been clearly established (Zapata et al. 1994). A peroxidase A from a *Vitis vinifera* Pollux 13 cell culture was also isolated, which could dimerize resveratrol into e-viniferin (Hoos and Blaich 1988). A basic peroxidase B5 isolated from *V. vinifera* Gamay Rouge was able to oxidize resveratrol, but the reaction products were not identified (Morales et al. 1997). This basic peroxidase B5 was identified in the hypodermal tissues and the mesocarp of *V. vinifera* cvs Airen and Monastrell as well, where it appears to be responsible for the oxidation of resveratrol (Calderon et al. 1994).

These results suggest that grapevine peroxidases can thus use resveratrol as a substrate (Table 1). However, they do not demonstrate the involvement of specific peroxidases in the grapevine defense responses to stress. Since peroxidases are not specific for their reductants (Hiraga et al. 2001), it thus remains to be seen whether these enzymes are specifically involved in stress defense reactions and the production of viniferins or if they just accept resveratrol as a common substrate under experimental conditions.

To elucidate the processes leading to the formation of the resveratrol dimers and the specific peroxidases involved, more recent studies focused on the relationship between peroxidase expression and resveratrol dimer production after exposition to various elicitors. Different elicitors have successfully led to the production of stilbenes in grapevine cell cultures. The most widely efficient elicitor is Methyl Jasmonate (MeJA), which enhances stilbene production along with stimulation of defense reactions (Belhadj et al. 2008; Taurino et al. 2015). However, as stilbenes are insoluble in culture media, they are rapidly degraded. Other elicitors such as cyclodextrins (CDs) have been shown to both stimulate the production and increase the stability of stilbenes (Bru et al. 2006; Lucas-Abellán et al. 2007; Nivelles et al. 2017a; Jeandet et al. 2021a). Proteomic studies carried out on *V. vinifera* Gamay cell cultures subjected to treatments with MeJA and/or methyl- $\beta$ -cyclodextrins evidenced an upregulation of certain peroxidases after elicitation (Martinez-Esteso et al. 2009). Although the formation of resveratrol dimers was not reported in this study, it is well known that these types of elicitors enhance resveratrol dimer production in grapevine cell cultures (Donnez et al. 2011; Santamaria et al. 2011; Lambert et al. 2019). Additionally, a transcriptomic approach on *V. vinifera* Monastrell cell cultures demonstrated that some peroxidases were up-regulated after elicitation with MeJA and CDs (Almagro et al. 2014).

Table 1 Identification and subcellular localization of grapevine peroxidases able to catalyze the conversion of resveratrol into its oligomers

Species/Variety	Peroxidases	Class	Subcellular localization	Compounds	Bioconversion rate (%)	References
<i>Vitis labruscana</i> L. cv. Campbell Early	APX6	I	Intracellular	d-viniferin	18.11	Park et al. (2021)
	GPX5	III	Secreted	d-viniferin	19.11	
	PRX13	III	Secreted	d-viniferin	22.33	
	PRX21	III	Secreted	d-viniferin	46.00	
	PRX35	III	Secreted	d-viniferin	41.44	
	PRX40	III	Secreted	d-viniferin	27.33	
	PRX50	III	Secreted	d-viniferin	18.22	
<i>Vitis vinifera</i> Pollux 113	Peroxidase A	na	Intracellular	e-viniferin	na	Hoos and Blaich (1988)
<i>Vitis vinifera</i> Gamay Rouge	Basic peroxidase isoenzyme B <sub>5</sub>	na	Intracellular (vacuolar)	na	na	Morales et al. (1997)
<i>Vitis vinifera</i> Monastrell and Airen	Peroxidase isoenzyme A1	na	Intracellular (cell wall)	na	na	Calderon et al. (1994)

na not available

The up-regulated peroxidases following these treatments (Martinez-Esteso et al. 2009; Almagro et al. 2014) seem to be specifically involved in the plant responses to stress and could be implied in resveratrol dimer formation. However, it remains to be proven whether these enzymes can use resveratrol as a substrate for dimer biosynthesis. Studies using *Vitis labruscana* cell cultures co-treated with MeJA and stevioside showed an accumulation of d-viniferin in the culture media (Jeong et al. 2020). This treatment was then used to track the expression of seven peroxidase-encoding genes namely, *VIAPX6* (Ascorbate peroxidase 6), *VIGPX5* (Glutathione peroxidase 5), *VIPRX13*, *VIPRX21*, *VIPRX35*, *VIPRX40* and *VIPRX50* which were selected for resveratrol bioconversion study after transient expression (Park et al. 2021). All these peroxidases were able to dimerize *trans*-resveratrol to d-viniferin (Table 1, Fig. 4). Interestingly, some of these peroxidases, especially *VIPRX21* and *VIPRX35* seemed to be more specific to resveratrol, thus displaying the highest bioconversion rate (Table 1). *VIAPX6* (ascorbate peroxidase 6) is specifically involved in cell protection against H<sub>2</sub>O<sub>2</sub> without showing any specificity for resveratrol (Caverzan et al. 2012). This peroxidase probably uses resveratrol only in *in vitro* experiments due to the non-specificity of peroxidases towards their reductant. It has been suggested that some peroxidases are specifically expressed after exposure to stress *in vivo*, and that some of them are more specific to resveratrol than others. This point needs to be further investigated.

The peroxidases identified as upregulated in these studies and associated with the biosynthesis of resveratrol dimers could be considered as potential markers for plant disease resistance. This is particularly relevant as most dimers seem to be more effective than their monomer, resveratrol, in controlling downy mildew disease (Pezet et al. 2004). In terms of bioproduction strategies, these grapevine peroxidases displaying a higher specificity for resveratrol could achieve higher yields or faster bioconversion reactions compared to HRP.

It is important to point out that most the studies have focused on the formation of the two dimers, d-viniferin and e-viniferin. However, the production of many other different dimers was reported in some elicited grapevine cell cultures (Fig. 4) (Nivelle et al. 2017a; Lambert et al. 2019). The pivotal question is whether a single peroxidase may be involved in the production of different resveratrol dimers and if so, what conditions might influence their production. For example, the pH could influence the nature of the dimers formed as previously described with HRP (Li et al. 2012; Jeandet et al. 2020).

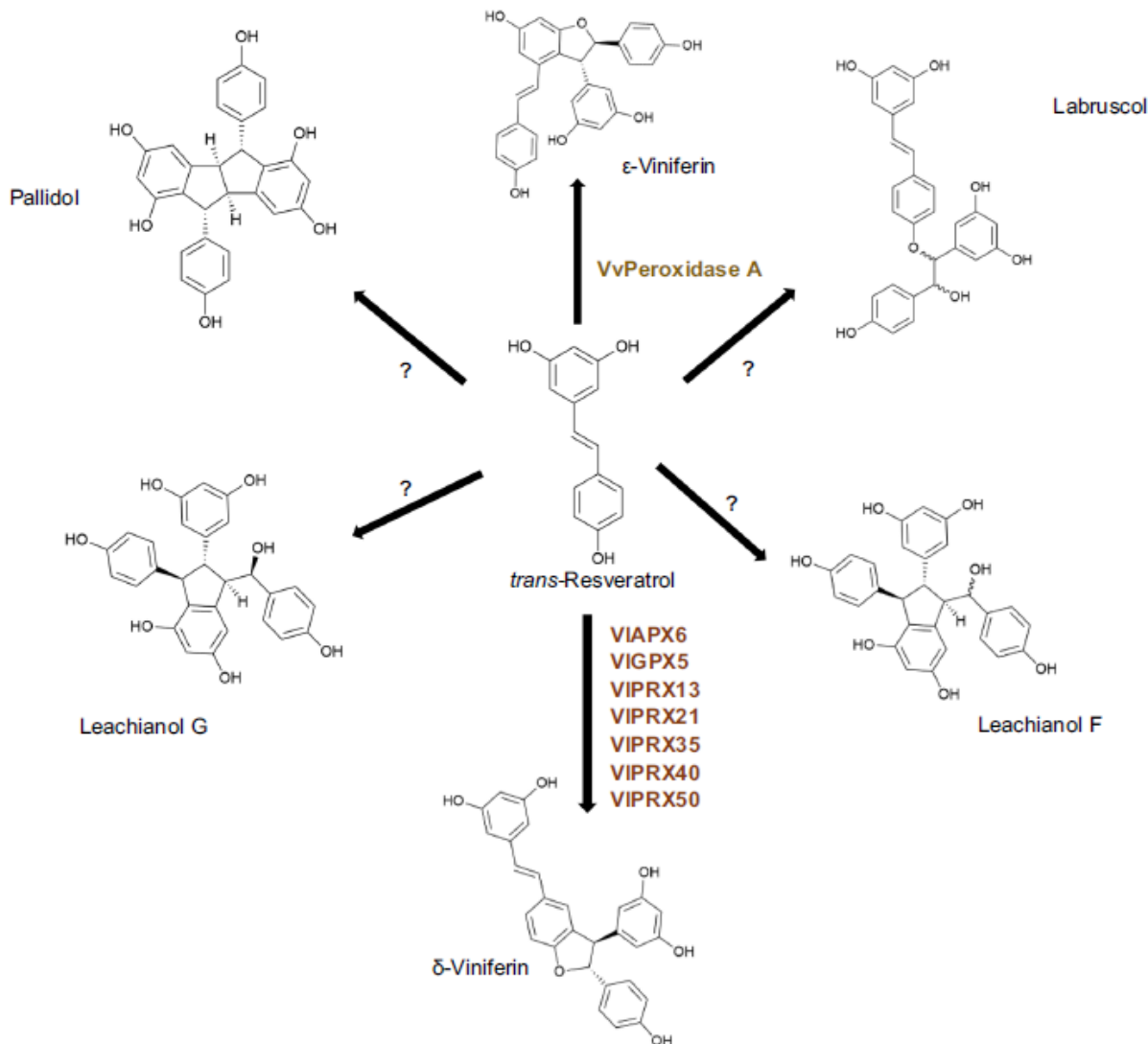


Fig. 4 Structure of some resveratrol dimers present in grapevine and their formation by identified grapevine peroxidases.  $\epsilon$ -Viniferin can be obtained by oxidative dimerization of resveratrol by peroxidase A, while  $\delta$ -viniferin synthesis required various peroxidases. The implication of peroxidases in the conversion of resveratrol to pallidol, labruscol, leachianol F and G remains to be investigated.

In fact, it is rather complicated to decipher the role played by peroxidases in the oligomerization processes of stilbenes. It is obvious that their functioning is at the genesis of resveratrol radicals (Fig. 5). Starting from this, Stephenson's group has brilliantly demonstrated that the formation of the oligomers proceeds according to various chemical condensation schemes of the radicals formed (Keylor et al. 2015). Figure 5 shows, for example, that the condensation of the two resveratrol radicals according to the 3–8<sup>0</sup> coupling (red bond) mode leads, after a rearomatization by intramolecular oxa-Michael type addition (blue arrows) and intra or intermolecular prototropies (green arrows), to the dihydrobenzofuran ring of  $\delta$ -viniferin. Similarly, the condensation of two resveratrol radicals according to the 8–8' coupling mode (red bond), followed by two symmetrical Friedel–Crafts reactions affords the bicyclic ring of pallidol (Fig. 5). Addition of water can also occur to allow rearomatization affording compounds such as Labruscol (Fig. 5).

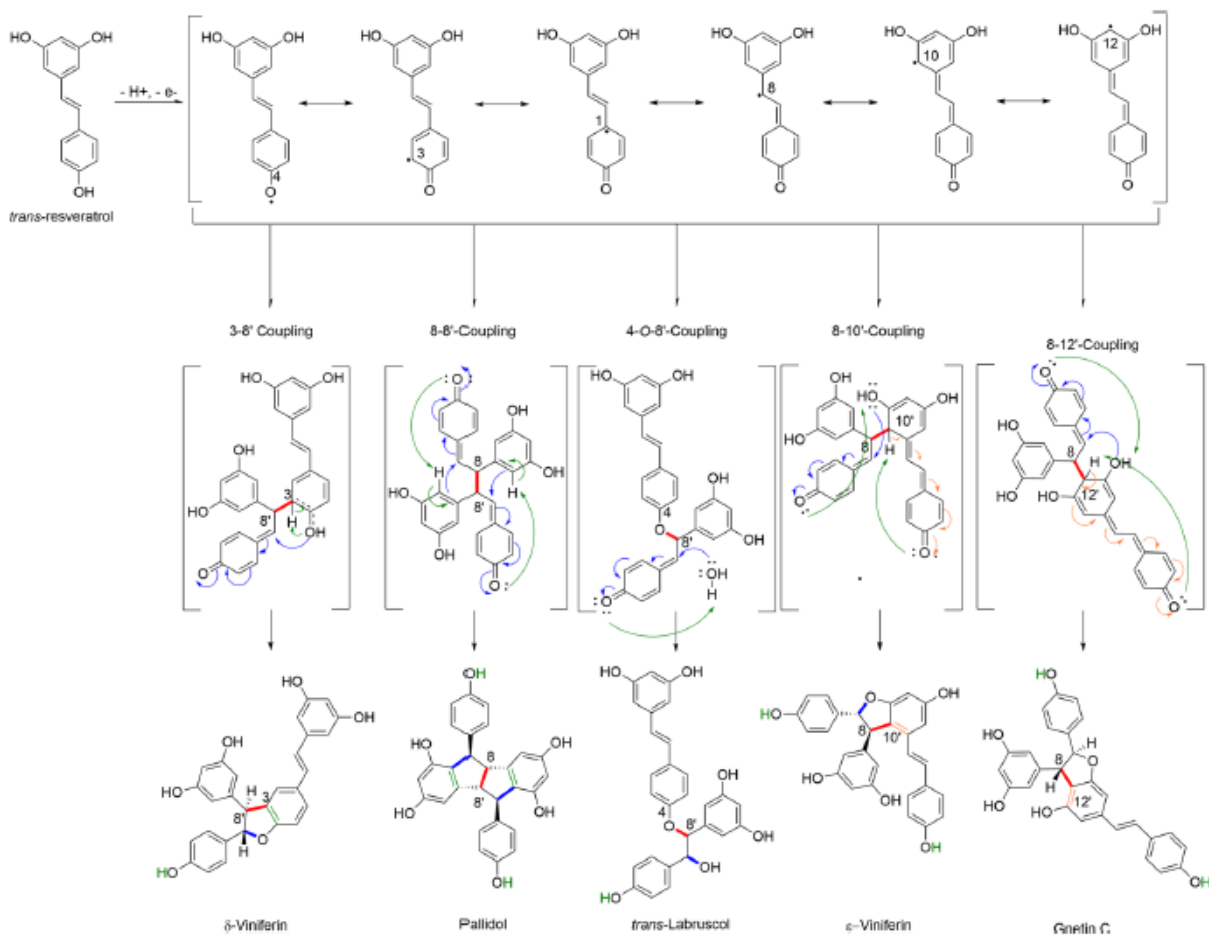


Fig. 5 Dimerization pathways of resveratrol through radical–radical coupling followed by rearomatization and prototropy mechanisms. Oxidation of resveratrol on the para-phenol moiety generated six radical positions. Multiple more or less favored couplings (red bond) can occur leading to the formation of various dimers after a rearomatization mediated by prototropies (green arrows)

The same reasoning allows access to almost all known structures of dimers. The question remains, however, open to know if the process of dimerization is entirely under chemical control or if the peroxidases make it possible to direct these syntheses. This raises the question of how the subsequent compounds of higher molecular order than dimers occurred. Here again, it is possible to decipher the formation of two grapevine trimers (gnetin H and miyabenol C) by condensation of two resveratrol radicals with two radicals formed from *e*-viniferin (Fig. 6). From there, two condensations according to the 10–8' and 8–10' modes of coupling, yield the two resveratrol trimers, gnetin H and miyabenol C, respectively (Keylor et al. 2015). Con- densation of two *e*-viniferin radicals according to the 3–8' homocoupling leads to the formation of resveratrol tetramers vitisin A and vitisin B.

Most of the studies have focused on the biosynthesis of dimers in grapevine, but the formation of the resveratrol trimers and tetramers remains to be eluci- dated. Resveratrol trimers and tetramers have been identified in *Vitis vinifera* canes (Goufo et al. 2020; Loupfit et al. 2020), but their presence failed to be demonstrated in grapevine cell cultures (Jeandet et al. 2023). Interestingly, vitisin B was identified in hairy root of *Vitis vinifera* cv Pinot Noir (Tisserant et al. 2016). In vitro experiments performed initially with two molecules of *e*-viniferin or using *e*-viniferin and resveratrol as substrates for HRP have successfully led to the formation of resveratrol trimers and tetramers (Takaya et al. 2002; He et al. 2008; Zhang et al. 2017). As the biosynthesis of resveratrol tetramers can be achieved through in vitro experiments with HRP, grapevine peroxidases would also be able to form resveratrol tetramers, in vitro. However, this has never been investigated with a grapevine peroxidase. As the resveratrol tetramers have not been identified in grape- vine cell cultures, thus specific grapevine enzymes produced locally may be responsible for tetramer formation, which could explain the production of these

molecules in grapevine stems but not in cell cultures.

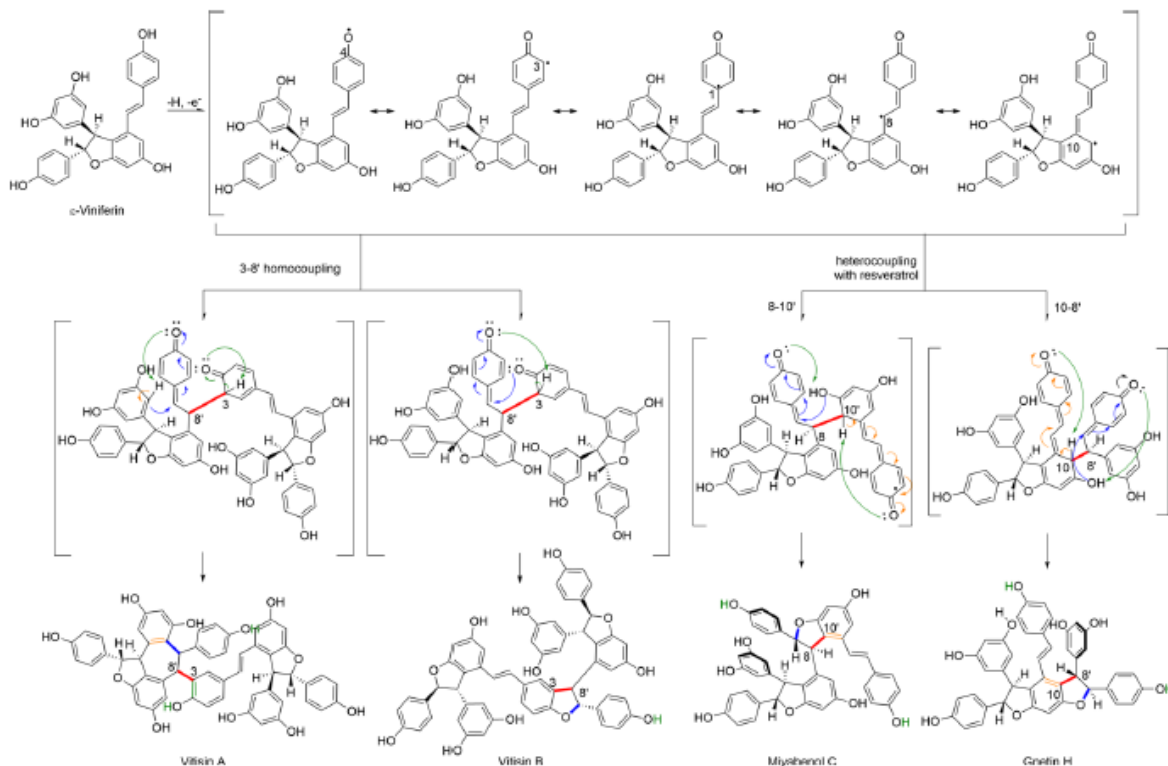


Fig. 6 Hypothetical homocoupling of  $\epsilon$ -viniferin leading to the tetramers vitisins A and B and heterocoupling with radical resveratrol leading to trimers miyabenol C and gnetin H. Oxidation on the conjugated para-phenolic moiety of  $\epsilon$ -viniferin generated five radical positions. The homocoupling of radical species 3 and 8 (red bond) led, after rearomatization (blue arrows) mediated by prototropies (green arrows) to two known tetramers vitisins A and B. The heterocoupling of  $\epsilon$ -viniferin radical 8 with resveratrol radical 10 produced the trimer, miyabenol C. The heterocoupling of  $\epsilon$ -viniferin radical 10 with resveratrol radical 8 produced the trimer, gnetin H.

## Laccases and formation of resveratrol dimers

Laccases (benzenediol:oxygen oxidoreductases, EC 1.10.3.2) are enzymes belonging to the Multi-Copper Oxidases (MCOs) enzyme family (Giardina et al. 2010). They were first isolated from *Rhus vernifera* (Hikorokuro 1883), and can oxidize a wide range of substrates, such as phenolic compounds, use oxygen and generate water (Arregui et al. 2019). Therefore, they are also classified as polyphenol oxidases (Mayer and Staples 2002; Hoegger et al. 2006). They can be found in plants, fungi, and prokaryotes. In plants, there are involved in the polymerization of lignins (Schuetz et al. 2014) and flavonoids (Pourcel et al. 2005; Wei et al. 2021).

Breuil et al. (1998) demonstrated for the first time the dimerization of resveratrol into a dehydrodimer further called d-viniferin, by a laccase from *B. cinerea*. Other studies then confirmed the dimerization of resveratrol by fungal laccases. In fact, other dimers such as pallidol, leachianol F and d-viniferin can be produced by *B. cinerea* laccases (Pezet 1998; Cichewicz et al. 2000). Pallidol and leachianol F and G were also produced from the incubation of resveratrol with extracellular proteins of *Diplodia seriata* and *Neofusicoccum parvum* (Labois et al. 2021).

Although a lot of experiments have described the formation of various stilbene dimers by fungal laccases in vitro, namely the laccases of *Myceliophora thermophyla*, *Trametes pubescens* (Nicotra et al. 2004; Ponzoni et al. 2007) as well as the laccases of *Trametes villosa* and *Trametes versicolor* (Zhang et al. 2012; Beneventi et al. 2015; Sursin et al. 2023), resveratrol dimerization by plant laccases has never been investigated.

Grapevine peroxidases are able to condense resveratrol suggesting that resveratrol dimers could also be produced by plant laccases as in the case of lignin or flavonoid metabolisms. In *V. vinifera*, 29 laccase-encoding genes have been identified (Liu et al. 2020). Most of these laccases are extracellular, but they are also found in mitochondria, lysosomes/vacuoles or in the cytoplasm. It could be interesting to investigate the expression of certain extracellular laccases after elicitation of grapevine cell cultures, as the production of stilbene dimers seems to occur in the culture media (Lambert et al. 2019). Heterologous expression of up-regulated laccases could validate their role in resveratrol oligomerization. Moreover, it is possible that a set of laccases and peroxidases could be involved together in the biosynthesis of dimers in grapevine although, to the best of our knowledge, this has not been demonstrated to date. Once the resveratrol core is formed, it can be modified by various enzymes called decorating enzymes leading to glycosylated, hydroxylated, methylated and prenylated resveratrol derivatives. As no prenylated forms of resveratrol have been reported to date in grapevine, we will focus on glycosyltransferases, hydroxylases and methyltransferases in the rest of this article.

## Glycosyltransferases and formation of glycosylated stilbenes

Glycosyltransferases (GTs) (EC 2.4) are enzymes that catalyze the transfer of sugars to an acceptor molecule. They are present in all living organisms: eukaryotes, prokaryotes, archaea, and viruses. GTs are classified into 114 families and subfamilies (GT1-GT114) (Zhang et al. 2022). Family 1 contains plant UDP-GTs (UGTs) which transfer uridine diphosphate activated sugars to secondary metabolites such as terpenes, alkaloids, phenols and other compounds (Zhang et al. 2022). They all contain a conserved 44-amino acid motif called the plant secondary product glycosyltransferases (PSPG) box (Le Roy et al. 2016). They are not specific to their substrates (Zhang et al. 2022). Glycosylation is one of the most widespread modification processes of secondary metabolites, making these enzymes increasingly studied in recent years. Indeed, glycosylation influences the stability, solubility, toxicity, and bioactivity of natural compounds (Zhang et al. 2022). In plants, glycosylation also regulates compartmentation and controls the vacuolar storage of toxic compounds under their glycosylated forms as well as their release and activation in the event of a pathogen attack (Jones and Vogt 2001). This phenomenon has been well described with monolignols (Le Roy et al. 2016) anthocyanins (Cheng et al. 2014) and linamarin (Vetter 2000). It has been suggested that the same regulatory procedure applies to piceid, a resveratrol glucoside (Chong et al. 2009), but the specific glycosylation process of its storage remains to be understood.

Glycosylated derivatives (*trans*-piceid, *cis*-piceid and *trans*-astringin) are produced in grapevine cell cultures after abiotic stress (Waffo Teguio et al. 1996a, b, 1998). However, piceid itself did not show any toxic activity against *P. viticola* zoospores (Pezet et al. 2004). This glycosylated derivative seems to be accumulated inside the cells, confirming that it can be released in case of a pathogen attack (Belhadj et al. 2008). There have been several attempts to identify GTs involved in resveratrol glycosylation in *Vitis* spp. Resveratrol was found to be glycosylated to piceid by a crude extract of intracellular enzymes from a *V. vinifera* cell culture (Krasnow and Murphy 2004). Moreover, a correlation between piceid production and *VaGlu1* (resveratrol-O-glycosyltransferase 1) gene expression in the leaves of *V. amurensis* was observed (Kiselev et al. 2017). However, the corresponding enzymes have not been isolated to test their specific glycosylating activity toward resveratrol (Kiselev et al. 2017). A glycosyltransferase (VLRSGt) has been isolated from the grape berries of *V. labrusca* able of glycosylating resveratrol into piceid (Hall and De Luca 2007). This enzyme shows 99.37% identity with the *VaGlu1* enzyme previously mentioned (Kiselev et al. 2017), supporting the hypothesis that *VaGlu1* could use resveratrol as a substrate. An interesting study on a UGT from *Vitis vinifera* (VvUGT72B27) showed that this enzyme can glycosylate resveratrol to both piceid and resveratrol-4-*O*-glucoside (Fig. 7) (Hartl et al. 2017). In *Vitis vinifera* cv Syrah, three functional genes coding for GTs were identified i.e., *VvgGT1*, *VvgGT2* and *VvgGT3*. Resveratrol was tested as a substrate on the purified enzymes, but none of the candidate enzymes could use it (Khater et al. 2012). These results are in contradiction with those obtained for *V. labrusca*. VvGT2 showing 99.35% homology with VLRSGt but cannot use resveratrol as a substrate in a similar pH range (Khater et al. 2012). Other enzymes isolated from *V. vinifera* can accept many different flavonoids as substrates, but resveratrol was not tested with these enzymes (Ono et al. 2010; De Bruyn et al. 2015).

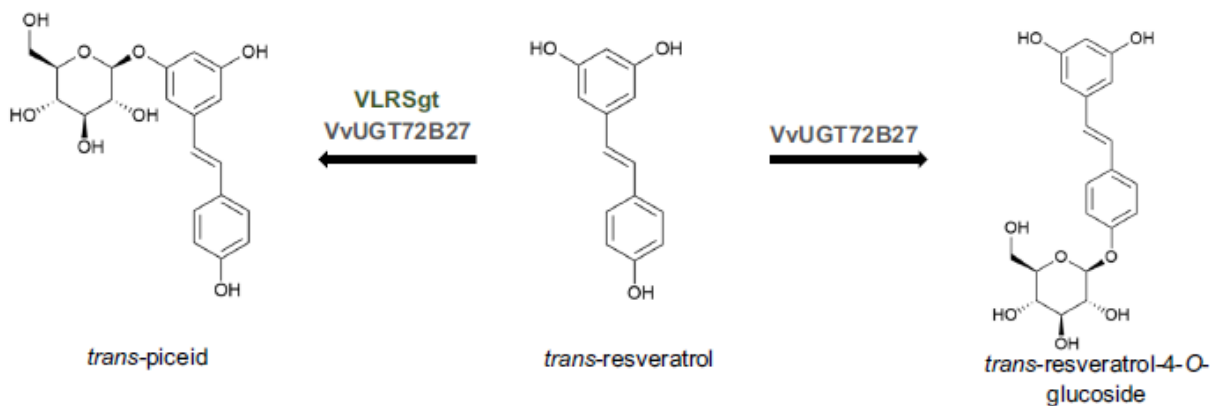


Fig. 7 Structures of resveratrol glycosylated derivatives produced in grapevine tissues by two identified grapevine glycosyltransferases (VLRSGt and VvUGT72B27).

In the *V. vinifera* genome, 240 *UGTs* genes have been identified (Jaillon et al. 2007), suggesting the existence of a multitude of glycosylation reactions. It is likely that several GTs are involved in the glycosylation of resveratrol, depending on substrate specificity. Piceid and anthocyanins are produced in large amounts in *V. vinifera* cv Gamay Teinturier Fréaux cell cultures (Waffo Teguo et al. 1996a). Some GTs could use both flavonoids and resveratrol as substrates in a nonspecific way depending on their availability. However, UGTs from *V. vinifera* cv Syrah show some selectivity for phenolic acids and did not use flavonoids and stilbenes as substrates (Khater et al. 2012). This is also supported by assays done with *V. vinifera* crude extracts containing GTs (Krasnow and Murphy 2004). However, the observed specificity could also come from the experimental conditions. Thus, it is still difficult to conclude on the involvement of specific grapevine GTs for the *in vivo* glycosylation of resveratrol.

The production of astringin, the 3-*O*- $\beta$ -D-glucoside of piceatannol, was not observed with the glycosyltransferases VLRSGt or VvUGT72B27, but the formation of this compound could result from a different process. Indeed, astringin is a stilbene both hydroxylated and glycosylated. The biosynthesis of this compound could involve either a primary glycosylation step of resveratrol to piceid followed by hydroxylation, or an initial hydroxylation of resveratrol to piceatannol followed by glycosylation. This reaction could be investigated by supplying piceatannol to VvUGT72B27 or VLRSGt to see if these enzymes accepted it as a substrate.

There are several studies reporting on the regulation of stilbene biosynthesis (for review see Jeandet et al. 2019, 2021b). Less is known about understanding the regulation of the GTs which seems quite complex. Indeed, since piceid is a storage form of resveratrol, GTs can be present at a basal level in the plant cell and use resveratrol when it is available. However, a regulation of this storage involving specific transcription factors (TFs) up-regulating the expression of resveratrol GTs could exist. There are some studies reporting on the regulation of the piceid content by TFs and hormones. For example, a correlation between the TFs MYB14 and MYB15 and piceid accumulation was noticed in *V. vinifera* grape berries (Holl et al. 2013). Overexpression of *MYB15* in grapevine hairy roots was accompanied by piceid accumulation and an upregulation of *STS29* and *STS41*. MYB15 could upregulate the GTs responsible for piceid production. Overexpression of the *VvABF2* gene, a basic leucine zipper transcription factor, in grapevine cell cultures treated with acid abscisic (ABA) showed an increase in piceid and resveratrol (Nicolas et al. 2014). However, these studies did not address GTs regulation.

Glycosylated derivatives are particularly attractive to the industry due to their enhanced bioavailability and water solubility compared to their aglycones (Lee et al. 2023). Concerning the bioproduction of glycosylated stilbenes, there have been fewer studies on heterologous production than for other stilbene derivatives (Jeandet et al. 2018). Nevertheless, an UGT YjiC from *Bacillus* spp. expressed in *Escherichia coli* has been used for the biosynthesis of several resveratrol glucoside derivatives, but low amounts (2.5 mg/L of piceid) were obtained (Choi et al. 2014). Enzymatic synthesis could be promising to obtain higher yields than production in heterologous systems, generating new derivatives (Marié et al. 2018; Moon et al. 2021), such as a-piceid, which exhibits better solubility than b-piceid (Moon et al. 2021). The use of more specific glycosyltransferases from *Vitis* spp. could

direct the bioconversion towards a specific type of derivative.

## Hydroxylases and formation of hydroxylated stilbenes

Hydroxylases belong to the plant cytochrome P450 (CYP450) family, which is the largest family of enzymes involved in hydroxylation reactions (Pandian et al. 2020). CYP450s are the main contributors to metabolite diversity thanks to their involvement in the biosynthesis of several defense compounds including terpenes, alkaloids, and flavonoids (Pandian et al. 2020). Indeed, hydroxylation is the most common modification occurring in natural flavonoids modulating their chemical properties and bioactivities (Liu et al. 2022). P450s are mainly located in the endoplasmic reticulum (Ro et al. 2002; Pandian et al. 2020). Within the flavonoid family, hydroxylation determines their coloration, stability, and antioxidant capacity (Forkmann 1991). Namely, enzymes such as a flavonoid 3'-hydroxylase (VvF3'H) and flavonoid 3<sup>0</sup>5' hydroxylase 1 (VvF3',5'H1) from *Vitis vinifera* are responsible for anthocyanin content and color in *V. vinifera* (Bogs et al. 2006).

The role of hydroxylated resveratrol derivatives, such as piceatannol in grapevine remains difficult to be elucidated because the latter was detected in low quantities in planta (Dubrovina and Kiselev 2017). This compound is produced in response to stress in grapevine (Dubrovina and Kiselev 2017), exhibiting antifungal activity against *Aspergillus carbonarius* (Bavaresco et al. 2003) and accumulating in grapevine woody tissues following bud burst (Noronha et al. 2023). Piceatannol shows less antimicrobial activity than its methylated derivative, isorhapontigenin, against *Plasmopara viticola* (Gabaston et al. 2017).

The biosynthetic pathway of this compound and its derivatives (astringin, isorhapontigenin) is still poorly understood (Kiselev et al. 2016). In *Picea* spp, three biological pathways have been proposed for the formation of piceatannol involving either a double hydroxylation of pinosylvin, the 3'-hydroxylation of resveratrol, or the condensation of caffeoyl-CoA with three malonyl-CoA units by the stilbene synthase (Kiselev et al. 2016). However, in vitro enzyme assays with the STS from *Picea* spp showed that this enzyme uses only *p*-coumaroyl-CoA as a substrate, excluding the hypothesis of a direct formation of piceatannol from caffeoyl-CoA (Hammerbacher et al. 2011). In *Vitis* spp, pinosylvin has not been identified (Bakrim et al. 2022) in contrast to piceatannol (Bavaresco et al. 2002), astringin (Waffo Teguog et al. 1998) and isorhapontigenin (Fernández-Marín et al. 2012). These facts further support the involvement of a 3'-hydroxylase in the biosynthesis of hydroxylated resveratrol derivatives (Fig. 8). However, to the best of our knowledge, there are no reports on specific hydroxylases involved in the hydroxylation process of resveratrol (Jeandet et al. 2021b).

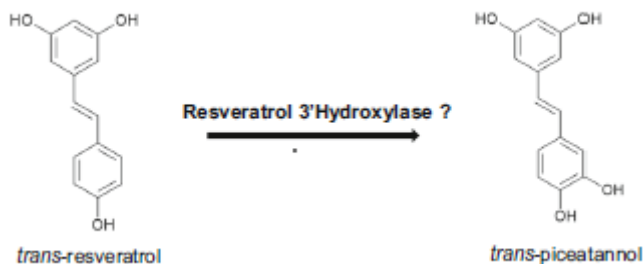


Fig. 8 Hypothetical formation of piceatannol (3,5,3',4'-tetrahydroxystilbene) from resveratrol through a reaction catalyzed by a resveratrol 3'hydroxylase.

Surprisingly, a non-specific resveratrol enzyme (non-P450 hydroxylase hpaBC from *Escherichia coli*) was found to allow the accumulation of piceatannol at high amounts (1,2 g/L) (Lin and Yan 2014).

## Methyltransferases and formation of methylated stilbenes

Methyltransferases (EC 2.1.1) are enzymes that catalyze the transfer of a methyl group onto an acceptor molecule. Among them, *O*-methyltransferases (OMTs) catalyze *O*-methylation reactions and use *S*-

adenosylmethionine (SAM) as a methyl group donor (Kim et al. 2010). OMTs are classified as class I or class II depending on their structure and properties: the caffeoyl-CoA OMT (CCoAOMT) type, which have low subunit molecular mass and a dependence on  $Mg^{2+}$ , and the caffeic acid OMT type (COMT), which have higher subunit molecular mass and do not require  $Mg^{2+}$  (Joshi and Chiang 1998; Kim et al. 2010; Itoh et al. 2016). *O*-methylation is a frequent modification of plant secondary metabolites, which modifies their properties, by increasing, for example, the antimicrobial activity of flavonoids (Kim et al. 2010) or by producing a rose scent with the molecule of 3,5-dimethoxytoluene, produced by an orcinol *O*-methyltransferase (Lavid et al. 2002).

In *Vitis* spp., the methylated resveratrol derivative, pterostilbene (3,5-dimethoxy-4'-resveratrol) displayed five times higher antifungal activity than resveratrol (Adrian et al. 1997), and is the most active stilbene compound produced by grapevine against *P. viticola* compared to resveratrol dimers (Langcake 1981). However, this compound is consistently found in low quantities or remains undetectable (Langcake et al. 1979; Langcake 1981; Jeandet et al. 1997; Schmidlin et al. 2008), making the study of its role particularly difficult in grapevine.

In Scots pine (*Pinus sylvestris*), pinosylvin (3,5-dihydroxystilbene) can be methylated by a pinosylvin-*O*-methyltransferase (PMT) to pinosylvin 3-*O*-methyl ether after an elicitation treatment (Chiron et al. 2000). In *V. vinifera* Cabernet Sauvignon, a resveratrol *O*-methyltransferase (ROMT) involved in the production of pterostilbene has been identified and characterized (Fig. 9) (Schmidlin et al. 2008). Enzyme's expression and pterostilbene production were induced by both abiotic (UV and  $AlCl_3$ ) and biotic (*P. viticola*) stresses.

As methyltransferases exhibit a high bioconversion efficiency, they have been used in many pterostilbene bioproduction strategies using heterologous systems (for reviews see Jeandet et al. 2018; Thapa et al. 2019). Indeed, the antimicrobial activity of methylated resveratrol derivatives is higher than that of their non-methylated counterparts. This could be particularly relevant for biocontrol applications and plant engineering regarding disease resistance (Zernova et al. 2014). Pterostilbene production using the *VvROMT* gene has also been achieved in engineered yeast and bacteria, resulting in the accumulation of 150 mg/L and 170 mg/L, respectively of this compound (Wang et al. 2015). In other studies, engineered mutants of ROMT were also able to produce pinostilbene (*trans*-3-methoxy-5,4'-dihydroxystilbene) (Herrera et al. 2021).

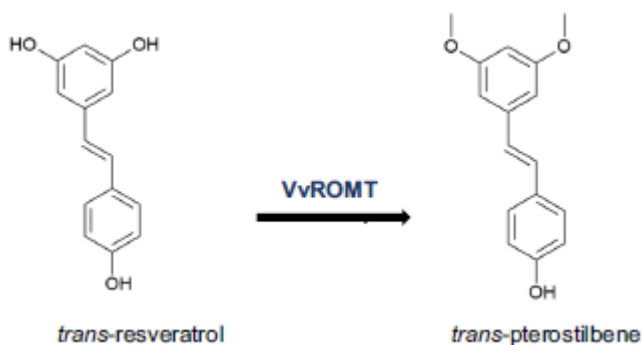


Fig. 9 Methylation reaction of resveratrol into pterostilbene mediated by VvROMT.

## Conclusions and perspectives

In this review, we discussed advances in the identification and understanding of the key enzymes involved in resveratrol dimerization/oligomerization, glycosylation, methylation, and hydroxylation in *Vitis* spp. All these resveratrol-based stilbenes are produced after plant exposure to various stresses. In total, thirteen enzymes of grapevine able of using resveratrol as a substrate have been identified, including ten peroxidases, two UGTs and one OMT. The diversity of resveratrol derivatives is also generated by other plant enzymes. Interestingly, several stilbenoid-specific prenyltransferases forming prenylated stilbenes have been described in peanut (*Arachis hypogaea*) (Yang et al. 2016). As mentioned before, the occurrence of this type of prenylated compounds has not been reported in grapevine.

The formation of resveratrol dimers/oligomers in *Vitis* spp. is well documented. Ten peroxidases have already

been identified, but several other peroxidase candidates, which are up-regulated in correlation with dimer formation in elicited grapevine cell cultures (Belhadj et al. 2008; Donnez et al. 2011) need to be investigated (Martinez-Esteso et al. 2009; Almagro et al. 2014). Putative grapevine laccases may also be involved in resveratrol dimer production, but these reactions have never been investigated. Elicited grapevine cell cultures represent a suitable system for the study of peroxidases, which could be extended to laccases since dimers are produced in large quantities in the extracellular medium. However, the occurrence of pterostilbene has never been reported in grapevine cell cultures (Bru et al. 2006; Lijavetzky et al. 2008; Martinez-Esteso et al. 2009; Martínez- Ma´rquez et al. 2016; Lambert et al. 2019), though a VvROMT has already been described in grapevine leaves (Schmidlin et al. 2008). In contrast, piceid is produced at a significant level in grapevine cell cultures, making this system suitable for studying GTs. However, GTs have so far only been studied in grape berries (mesocarp) (Hall and De Luca 2007), petioles and leaves (Kiselev et al. 2017). It could be interesting to examine the expression of GTs in grapevine cell cultures where a high production of piceid is induced by elicitors (Belhadj et al. 2008). To our knowledge, grapevine cell cultures that produce piceid always form anthocyanins. Piceid formation could thus be linked to anthocyanin biosynthesis, which are highly glycosylated compounds. Finally, the biosynthesis of piceatannol remains to be elucidated because no enzyme able of directly hydroxylating the resveratrol core is clearly identified, even if current observations support the involvement of a resveratrol 3'-hydroxylase (Hammerbacher et al. 2011; Kiselev et al. 2016). Piceatannol was identified in grapevine cell cultures in small amounts (Donnez et al. 2011) making it difficult to study piceatannol formation in this system. Lastly, an exciting challenge would be to decipher the role of peroxidases in the oligomerization process of resveratrol and whether these enzymes are able to orientate this process for the production of specific oligomers.

The limit of the exposed results appears to be the *in vitro* bias, where enzymes accept many substrates and where the test conditions do not reflect what happens *in vivo*. Thus, some enzymes may not accept the substrates *in vitro* as that they normally do use *in vivo*. CRISPR/Cas9-directed mutagenesis on the genes coding for the identified enzymes would confirm their role *in vivo*. This genome editing approach is also suitable for grapevine cell cultures (Wang et al. 2018; Ren et al. 2019).

Finally, identification of the enzymes involved in the formation of resveratrol derivatives in *Vitis* spp. could bring interesting perspectives for stilbene bio- production. Ideally, the specific enzymes of the synthesis of one type of derivatives could be selectively stimulated by elicitors in grapevine cell culture. These enzymes would also lead to higher production yield of resveratrol derivatives using heterologous systems.

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**Conflict of interest** The author declares no conflicts of interest.

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