



General and specialized tyrosine metabolism pathways in plants

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Received: 30 May 2019 / Accepted: 6 August 2019 / Published online: 6 September 2019

Abstract The tyrosine metabolism pathway serves as a starting point for the production of a variety of structurally diverse natural compounds in plants, such as tocopherols, plastoquinone, ubiquinone, betalains, salidroside, benzyloquinoline alkaloids, and so on. Among these, tyrosine-derived metabolites, tocopherols, plastoquinone, and ubiquinone are essential to plant survival. In addition, this pathway provides us essential micronutrients (e.g., vitamin E and ubiquinone) and medicine (e.g., morphine, salidroside, and salvianolic acid B). However, our knowledge of the plant tyrosine metabolism pathway remains rudimentary, and genes encoding the pathway enzymes have not been fully defined. In this review, we summarize and discuss recent advances in the tyrosine metabolism pathway, key enzymes, and important tyrosine-derived metabolites in plants.

Keywords Tyrosine, Tyrosine-derived metabolites, Secondary metabolism, Plants

INTRODUCTION

In plants, tyrosine is synthesized de novo via the shikimate pathway, which also gives rise to the other two aromatic amino acids, phenylalanine and tryptophan (Maeda and Dudareva 2012). Besides proteinogenic, tyrosine is a biosynthetic precursor of tocopherols, plastoquinone, and ubiquinone that are essential to plant itself. Furthermore, tyrosine is used as a substrate to synthesize numerous specialized metabolites in different groups of plants, such as rosmarinic acid (RA) and its derivatives in the families of Lamiaceae and Boraginaceae (Petersen and Simmonds

2003), dhurrin in *Sorghum*, salidroside in *Rhodiola*, betalains in the Caryophyllales order, benzyloquinoline alkaloids in the Ranunculales order (Liscombe et al. 2005), amaryllidaceae alkaloids in the family of Amaryllidaceae (Kilgore and Kutchan 2016), emetine alkaloids in the families of Alangiaceae, Icacinaceae, and Rubiaceae (Wiegrebbe et al. 1984), phenylethylamines like mescaline in cactus species (Cassels and Saez-Briónes 2018), phenethylisoquinoline alkaloids like colchicine in *Colchicum* (Rinner and Waser 2016), and catecholamines in a long list of plant species (Kulma and Szopa 2007). The importance of tyrosine-derived plant metabolites for both plant survival and human health has attracted great interests in elucidation of their biosynthetic pathways.

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In plants, tyrosine can be modified by different enzymes to yield specific types of the tyrosine-derived metabolites, of which the distributions, functions, and practical uses have been recently reviewed (Schenck and Maeda 2018). In this short review, we focus on the biosynthetic pathways of tyrosine-derived metabolites in plants. We propose a concept of the general tyrosine metabolism pathway, which is common in plants. We also discuss key enzymes of tyrosine metabolism, which catalyze committed steps in the biosynthesis of tyrosine-derived specialized metabolites.

THE GENERAL TYROSINE METABOLISM PATHWAY

The amino acid tyrosine provides the core cyclic scaffold to tocopherols, plastoquinone, and ubiquinone, which are synthesized in all plants (Fig. 1). Tocopherols, together with tocotrienols, form a group of lipid soluble antioxidants termed tocochromanols, which play a number of physiological roles in plants beyond antioxidant (Munné-Bosch and Alegre 2002; Falk and Munne-Bosch 2010). Tocochromanols are commonly known as vitamin E and are essential components of our nutrition. Unlike tocopherols, the tocotrienols are not as widespread as tocopherols (Horvath et al. 2006), and contain three double bonds in the isoprenoid side chain. Plastoquinone is found in all green lineages, ranging from cyanobacteria and algae to land plants, and acts as electron transporter in photophosphorylation, thus is indispensable to plant growth. Ubiquinone, also known as Coenzyme Q (CoQ), is an isoprenoid quinone produced in almost all living organisms and functions as electron transporter in the respiratory chain. Ubiquinone, which is now widely used as a food supplement, is often termed vitamin Q (Shukla and Dubey 2018; Pravst et al. 2010). The benzene quinone ring of ubiquinone is thought to be derived from 4-hydroxybenzoic acid (4-HB), whereas the ring precursor for tocopherols and plastoquinone is homogentisic acid (HGA). The remaining steps for the biosynthesis of tocopherols, plastoquinone, and ubiquinone have been reviewed elsewhere (Liu and Lu 2016; Mene-Saffrane 2017; Fritsche et al. 2017); this section will summarize metabolic origins of the HGA and 4-HB, which are key intermediates of the general tyrosine metabolism pathway.

Tyrosine aminotransferase (TAT; EC 2.6.1.5) catalyzes the reversible transamination from tyrosine to form 4-hydroxyphenylpyruvic acid (pHPP), an initial step of the tyrosine conversion. The aminotransferase activity depends on pyridoxal-5'-phosphate. TAT homologs are likely widely distributed in plants (Fig. 2A). In most

plant species, TAT catalyzes the removal of the amino group of tyrosine (Wang et al. 2016, 2019; Wang and Maeda 2018). An exception is that in legumes, which have a non-plastidic prephenate dehydrogenase (PDH, EC 1.3.1.13) that converts prephenate into pHPP, TAT is assumed to catalyze the transamination of pHPP to synthesize tyrosine (Schenck et al. 2015). However, the *in planta* role of TAT in tyrosine biosynthesis has not been clearly demonstrated (Maeda and Dudareva 2012). In *Arabidopsis thaliana*, there are at least two genes encoding TAT (Table 1), *tat1* mutants have decreased tocopherol levels (Riewe et al. 2012), and a *tat1 tat2* double mutant accumulates less tocopherols than the *tat1* mutant under high-light stress (Wang et al. 2019), indicating that both TAT1 and TAT2 contribute to the biosynthesis of tocopherols. TAT is also involved in the biosynthesis of many other tyrosine-derived metabolites. For instance, an opium poppy (*Papaver somniferum*) TAT was shown to participate in the production of benzyloisoquinoline alkaloids, including morphine and codeine (Lee and Facchini 2011). In *Prunella vulgaris*, a Traditional Chinese Medicinal (TCM) plant in the family of Lamiaceae, TAT is involved in the biosynthesis of RA (Ru et al. 2017).

Following the formation by TAT, pHPP can be converted to HGA by 4-hydroxyphenylpyruvate dioxygenase (HPPD, EC 1.13.11.27), a member of the large family of non-heme iron α -ketoglutarate-dependent dioxygenases. This complex reaction involves decarboxylation, aromatic hydroxylation, and substituent migration in a single catalytic cycle (Fig. 1). This transformation seems unique in nearly all aerobic organisms (Moran 2005), and HPPD homologs were found in a wide range of plant species (Fig. 2B). In animals, HPPD is required to modulate blood tyrosine levels, while in plants, it plays a key role in production of the aromatic precursor of tocopherols and plastoquinone. As plastoquinone is essential to photosynthetic organisms (Munné-Bosch and Alegre 2002; Norris et al. 1995; Amesz 1973), HPPD is a target for the development of herbicides (Beaudegnies et al. 2009; Ndikurayo et al. 2017). In *Arabidopsis*, the loss-of-function mutation of HPPD led to tocopherol and plastoquinone deficiency (Norris et al. 1995, 1998). The availability of HGA limits tocochromanol production at least in some plant species and organs. For example, de-regulated HGA accumulation by co-overexpression of *Arabidopsis* HPPD and microbial enzymes such as *Escherichia coli* bifunctional chorismate mutase/prephenate dehydrogenase (TyrA) or *Saccharomyces cerevisiae* prephenate dehydrogenase (TYR1) in tobacco and *Arabidopsis* resulted in high levels of tocochromanol accumulation (Rippert et al. 2004; Zhang et al. 2013). In soybean, the

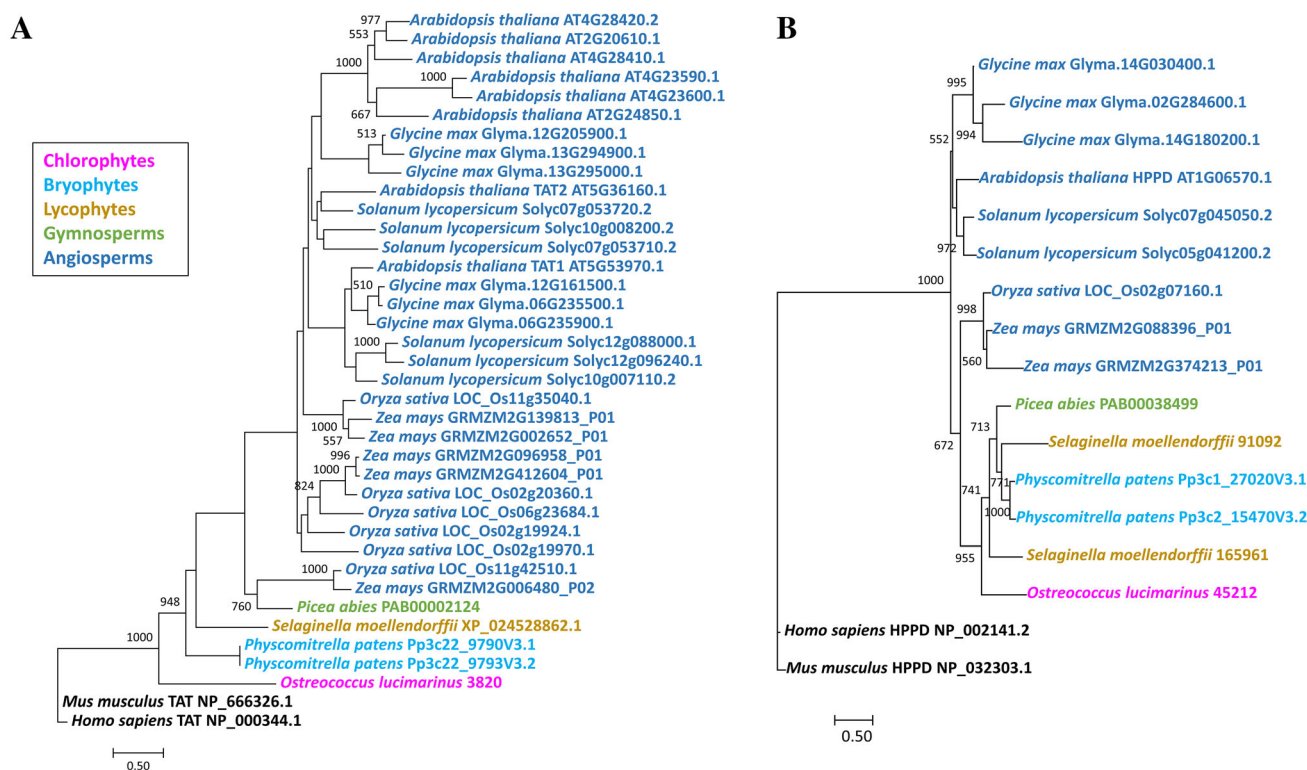


Fig. 2 Phylogenetic analysis of plant tyrosine aminotransferase (**A**) and 4-hydroxyphenylpyruvate dioxygenase (**B**). Amino acid sequences were aligned by ClustalX (Thompson et al. 1997) and the trees were generated in PhyML (Guindon et al. 2010) using maximum-likelihood method (1000 bootstrap replication). Bootstrap values less than 500 are not shown. The sequences of *Homo sapiens* and *Mus musculus* were used as outgroups. (**A**) The TAT sequences of *Homo sapiens*, *Mus musculus*, and *Selaginella moellendorffii* were obtained from NCBI, the protein sequences of *Picea abies* were from the PLAZA project (Van Bel et al. 2018), and the others were obtained via Phytozome v12 (Goodstein et al. 2012). (**B**) The HPPD sequences of *Homo sapiens* and *Mus musculus* were obtained from NCBI, the protein sequences of *Picea abies* were from the PLAZA project, and the others were obtained via Phytozome v12

mutant of *HGO1*, which encodes a homogentisate dioxygenase that breaks down HGA, overaccumulated HGA and tocochromanol (Stacey et al. 2016).

The 1,4-benzoquinone ring precursor for ubiquinone 4-HB is derived from tyrosine and phenylalanine in plants (Block et al. 2014). Significant progresses have been made recently in characterization of the biosynthesis of 4-HB from phenylalanine (Block et al. 2014; Soubeyrand et al. 2018); by contrast, much less is known about the generation of 4-HB from tyrosine. In *S. cerevisiae*, the first and last reactions of this pathway, namely the deamination of tyrosine to pHPP and the oxidation of 4-hydroxybenzaldehyde to 4-HB, have been characterized recently (Payet et al. 2016; Stefely et al. 2016); however, the evidence that TAT is involved in 4-HB formation is still lacking in plants. The endogenous levels of 4-HB may limit the ubiquinone production, since elevation in its pool has reported to have a positive effect on ubiquinone biosynthesis in *Arabidopsis* and tomato (Block et al. 2014; Soubeyrand et al. 2018). Further investigation of the tyrosine-derived metabolites and their connection to the

phenylpropanoid pathway would provide new insights into the ubiquinone biosynthesis and help to improve nutritional value of crop products.

BIOSYNTHESIS OF TYROSINE-DERIVED SPECIALIZED METABOLITES

Hydroxyphenylpyruvate reductase (HPPR, EC 1.1.1.237) catalyzes the reduction of pHPP to 4-hydroxyphenyl-lactic acid (pHPL), the precursor to rosmarinic acid (RA) (Petersen and Alfermann 1988; Häusler et al. 1991), which is frequently found in plants of the families Lamiaceae and Boraginaceae, with random reports of its presence in other families (Petersen and Simmonds 2003; Petersen 2013; Petersen et al. 2009). Chemically, RA is an ester of caffeic acid and 3,4-dihydroxyphenyl-lactic acid. More complex derivatives of RA have been identified, e.g., salvianolic acid B and other salvianolic acids from *Salvia* (Wu et al. 2012), and rabsosiiin from *Rabdosia japonica*. The HPPR enzyme was first isolated and characterized in *Coleus blumei* (*Plectranthus*

Table 1 Genes involved in tyrosine metabolism pathways in plants

Gene	Function	Organism	References
<i>AtTAT1</i>	Tyrosine aminotransferase	<i>Arabidopsis thaliana</i>	Wang et al. (2016, 2019), Riewe et al. (2012)
<i>AtTAT2</i>	Tyrosine aminotransferase	<i>Arabidopsis thaliana</i>	Wang et al. (2016, 2019)
<i>PstTAT</i>	Tyrosine aminotransferase	<i>Papaver somniferum</i>	Lee and Facchini (2011)
<i>PvTAT</i>	Tyrosine aminotransferase	<i>Prunella vulgaris</i>	Ru et al. (2017)
<i>AtHPPD</i>	4-Hydroxyphenylpyruvate dioxxygenase	<i>Arabidopsis thaliana</i>	Norris et al. (1995, 1998)
<i>AtHPPR2</i>	Hydroxyphenylpyruvate reductase	<i>Arabidopsis thaliana</i>	Xu et al. (2018)
<i>AtHPPR3</i>	Hydroxyphenylpyruvate reductase	<i>Arabidopsis thaliana</i>	Xu et al. (2018)
<i>CbHPPR</i>	Hydroxyphenylpyruvate reductase	<i>Coleus blumei</i>	Petersen and Alfermann (1988), Häusler et al. (1991)
<i>BdPTAL</i>	Phenylalanine/tyrosine ammonia-lyase	<i>Brachypodium distachyon</i>	Barros et al. (2016)
<i>CYP79A1</i>	Tyrosine <i>N</i> -monooxygenase	<i>Sorghum bicolor</i>	Koch et al. (1995), Sibbesen et al. (1995), Clausen et al. (2015)
<i>JrPPO</i>	Polyphenol oxidase	<i>Juglans regia</i>	Araji et al. (2014)
<i>CYP76AD1</i>	Tyrosine hydroxylase	<i>Beta vulgaris</i>	Hatlestad et al. (2012)
<i>CYP76AD5</i>	Tyrosine hydroxylase	<i>Beta vulgaris</i>	Sunnadeniya et al. (2016)
<i>CYP76AD6</i>	Tyrosine hydroxylase	<i>Beta vulgaris</i>	Polturak et al. (2016)
<i>PstTYDC1</i>	L-Tyrosine decarboxylase	<i>Papaver somniferum</i>	Facchini and De Luca (1995)
<i>PstTYDC2</i>	L-Tyrosine decarboxylase	<i>Papaver somniferum</i>	Facchini and De Luca (1995)
<i>AtTYDC</i>	L-Tyrosine decarboxylase	<i>Arabidopsis thaliana</i>	Lehmann and Pollmann (2009)
<i>OsTYDC</i>	L-Tyrosine decarboxylase	<i>Oryza sativa</i>	Kang et al. (2007)
<i>Rr4HPAAS</i>	4-Hydroxyphenylacetaldehyde synthase	<i>Rhodiola rosea</i>	Torrens-Spence et al. (2018)
<i>Pc4HPAAS</i>	4-Hydroxyphenylacetaldehyde synthase	<i>Petroselinum crispum</i>	Torrens-Spence et al. (2012)

scutellarioides) (Petersen and Alfermann 1988; Häusler et al. 1991). Recently, HPPRs from *Arabidopsis* were characterized (Xu et al. 2018), although RA is undetectable in this species (Petersen et al. 2009). Since HPPR is widely distributed in land plants rather than specific to RA-accumulating plants, pHPL could be converted into different types of natural products depending on the plant taxa, which deserves further investigation.

A subset of the phenylalanine ammonia-lyase (PAL, EC 4.3.1.24) enzymes in monocots also possess tyrosine ammonia-lyase (TAL, EC 4.3.1.23) activity, leading to the non-oxidative deamination of tyrosine to yield 4-coumaric acid. The TAL activity was found thus far particularly in monocots (Rosler et al. 1997; Barros et al. 2016; Jun et al. 2018; Cass et al. 2015; Beaudoin-Eagan and Thorpe 1985). In *Brachypodium distachyon*, a single bifunctional phenylalanine/tyrosine ammonia-lyase (PTAL) displays both PAL and TAL activities, the latter leading to the conversion of tyrosine to 4-coumaric acid, which is ultimately integrated into the phenylpropanoid-derived compounds such as lignin and flavonoids (Barros et al. 2016). The discovery of TAL

provides an alternative approach to optimize the production of phenylpropanoid compounds and tyrosine-derived metabolites. Enzymes that demonstrate specificity for tyrosine are referred to as TAL, which has been found in a number of microorganisms, such as *Rhodobacter capsulatus* (Kyndt et al. 2002), *Rhodobacter sphaeroides* (Watts et al. 2006), and *Saccharothrix espanaensis* (Berner et al. 2006). Replacing the active site residue His 89 with Phe can transform the *Rhodobacter sphaeroides* TAL into a highly active PAL and vice versa (Watts et al. 2006; Louie et al. 2006). The corresponding His residue is also critical for TAL activity in plants (Jun et al. 2018).

CYP79A1 catalyzes the multistep conversion of tyrosine into (*E*)-*p*-hydroxyphenylacetaldoxime (Koch et al. 1995; Sibbesen et al. 1995; Clausen et al. 2015), which is subsequently modified by CYP71E1 and a UDP (uridine diphosphate)-glucosyltransferase (UGT85B1) to produce dhurrin (Bak et al. 1998; Kahn et al. 1997; Jones et al. 1999; Laursen et al. 2016). Dhurrin, a defense cyanogenic glycoside mainly found in sorghum, has a strong insecticidal activity (Tattersall et al. 2001). Notably, enzymes of the dhurrin biosynthetic pathway

are assembled in a metabolon (Laursen et al. 2016; Nielsen et al. 2008).

Hydroxylation of tyrosine at 3-position leads to the formation of 3,4-dihydroxy-L-phenylalanine (L-DOPA). This reaction can be catalyzed by the tyrosinase (EC 1.14.18.1) activity of polyphenol oxidases (PPOs), which are widely distributed in microorganisms, animals, and plants. Interestingly, PPOs are absent from the genus of *Arabidopsis* (Tran et al. 2012). In walnut (*Juglans regia*), the PPO-silenced transgenic plant displayed a decrease in L-DOPA-derived metabolites and an increase in tyramine, demonstrating that the walnut PPO catalyzes the 3-hydroxylation of tyrosine (Araji et al. 2014). L-DOPA is also a precursor for the biosynthesis of betalains, however, whether PPO is involved in betalain biosynthesis remains an open question. It seems more likely that in betalain-producing plants, the 3-hydroxylation of tyrosine is catalyzed by a P450 monooxygenase, CYP76AD1, CYP76AD5, or CYP76AD6 (Sunnadeniya et al. 2016; Polturak et al. 2016; Hatlestad et al. 2012). The biosynthesis of betalain pigments has been recently reviewed (Polturak and Aharoni 2018).

L-Tyrosine decarboxylase (TYDC, EC 4.1.1.25) catalyzes the pyridoxal-5'-phosphate dependent decarboxylation of tyrosine and L-DOPA to yield tyramine and dopamine, respectively (Facchini and De Luca 1994, 1995). TYDC has been characterized from a variety of plant species (Facchini and De Luca 1994, 1995; Lehmann and Pollmann 2009; Torrens-Spence et al. 2013; Kang et al. 2007) and is assumed to be nearly ubiquitous among plants (Lehmann and Pollmann 2009). Notably, tyramine exhibits toxicity toward plants (Negrel et al. 1993; Christou and Barton 1989). For example, overexpression of TYDC in rice led to tyramine accumulation and stunted growth (Kang et al. 2007). Similarly, treatment of walnut leaves with exogenous tyramine induced the development of necrotic lesions (Araji et al. 2014). Tyramine is a precursor for the biosynthesis of hydroxycinnamic acid amides (e.g., feruloyltyramine) (Facchini et al. 2002) and amaryllidaceae alkaloids (e.g., lycorine) (Kilgore and Kutchan 2016).

Dopamine is an important neurotransmitter in the brain, and in plants, it is a precursor of numerous specialized metabolites, including phenethylisoquinoline alkaloids (e.g., colchicine) (Polturak and Aharoni 2018; Ehrenworth and Peralta-Yahya 2017), emetine alkaloids (e.g., emetine) (Nomura and Kutchan 2010), benzylisoquinoline alkaloids (e.g., morphine) (Schlager and Dräger 2016; Liu et al. 2017), catecholamines (e.g., epinephrine), and phenylethylamines (e.g., mescaline) (Rinner and Waser 2016). Dopamine can be synthesized via 3-hydroxylation of tyramine or decarboxylation of

L-DOPA, but enzymes responsible for the 3-hydroxylation of tyrosine or tyramine are still unclear in plants. In walnut, PPO is involved in the biosynthesis of dopamine (Araji et al. 2014); however, whether PPO plays a similar role in other plants awaits investigation. The predominant biosynthetic pathway of dopamine has not been identified, since TYDC has been shown to accept both tyrosine and L-DOPA as substrates. In human hydroxylation precedes decarboxylation in the major biosynthetic pathway of dopamine (Meiser et al. 2013).

Tyrosine is also converted to 4-hydroxyphenylacetaldehyde (4-HPAA) through decarboxylation-oxidative deamination, which is catalyzed by 4-hydroxyphenylacetaldehyde synthase (4HPAAS, EC 4.1.1.108) (Torrens-Spence et al. 2012, 2018a). 4-HPAA is a key intermediate in the biosynthesis of benzylisoquinoline alkaloids (e.g., morphine in Opium poppy) and tyrosol-derived specialized metabolites (e.g., salidroside in *Rhodiola*). In the biosynthesis of benzylisoquinoline alkaloids, 4-HPAA is proposed to be generated from tyrosine via TAT and an unidentified 4-hydroxyphenylpyruvate decarboxylase, respectively (Lee and Facchini 2011). Whether 4HPAAS, which directly converts tyrosine to 4-HPAA in *Rhodiola*, functions similarly in the benzylisoquinoline alkaloid metabolism is unclear. 4HPAAS belongs to the plant aromatic amino acid decarboxylase (AAAD) family (Facchini et al. 2000), of which other members include TYDC, tryptophan decarboxylase (TDC), and phenylacetaldehyde synthase (PAAS) (Torrens-Spence et al. 2018b). A single amino acid substitution of plant AAADs is capable of impacting substrate selectivity or altering catalytic reactions (Torrens-Spence et al. 2013, 2014, 2018b).

CONCLUSION AND PERSPECTIVES

Tyrosine serves as a biosynthetic precursor of a wide range of metabolites, many of which are of great nutritional, pharmacologic, and economic importance. Tocopherols and ubiquinone are vitamins essential to nearly all domains of life. Many benzylisoquinoline alkaloids possess potent pharmacological activities, including morphine and codeine (narcotic analgesics), noscapine (antitussive drug), papaverine (antispasmodic drug), and so on. RA and its derivatives have health-promoting properties, such as cardioprotection, antioxidant, antibacterial, and antiinflammatory activities (Bulgakov et al. 2012).

Considering the great diversity of tyrosine-related natural products in plants, the recent significant achievements in the biosynthetic pathways of the tyrosine-originated metabolites are just new beginnings of

further investigation. Many questions and knowledge gaps remain. For one example, none of the enzymes responsible for 4-HB production from tyrosine has been identified in the plant general tyrosine metabolism pathway. Definitely, better understanding of the tyrosine metabolism pathways will facilitate the breeding of high nutritional crop varieties and improving the production of valuable natural metabolites in plants.

Acknowledgements This project was supported by the Special Fund for Shanghai Landscaping Administration Bureau Program (Grant nos. G192416 and G192419).

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