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MINI-REVIEW

4-Hydroxybenzoic acid—a versatile platform intermediate for value-added compounds

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Abstract

4-Hydroxybenzoic acid (4-HBA) has recently emerged as a promising intermediate for several value-added bioproducts with potential biotechnological applications in food, cosmetics, pharmacy, fungicides, etc. Over the past years, a variety of biosynthetic techniques have been developed for producing the 4-HBA and 4-HBA-based products. At this juncture, synthetic biology and metabolic engineering approaches enabled the biosynthesis of 4-HBA to address the increasing demand for high-value bioproducts. This review summarizes the biosynthesis of a variety of industrially pertinent compounds such as resveratrol, muconic acid, gastrodin, xiamenmycin, and vanillyl alcohol using 4-HBA as the starting feedstock. Moreover, potential research activities with a close-up look at the future perspectives to produce new compounds using 4-HBA have also been discussed.

Keywords 4-Hydroxybenzoic acid · Platform intermediate · Synthetic biology · Metabolic engineering · Bioproducts

Introduction

The aromatic hydroxy acid, 4-hydroxybenzoic acid (4-HBA), is a valuable intermediate for the synthesis of several bioproducts with potential applications in food, cosmetics, pharmacy, fungicides, etc. It is a key component in the manufacturing of high-performance liquid crystal polymers (LCPs) with wider and ever-increasing applications in the thermoplastic industry (Ibeh 2011). The current production of 4-HBA is entirely based on petroleum-derived chemicals. However, the harsh reaction's conditions (high temperature and pressure), along with undesirable by-product generation, make the chemical process relatively expensive and unfavorable (Yoshida and Nagasawa 2007). Moreover, the limited raw material availability and high costs, together with environmental concerns necessitated the development of an economic and environmentally friendly bioprocess for aromatic 4-HBA biosynthesis (Gavrilescu 2014; Yu et al. 2016). In this context, several important bioproducts are produced from 4-HBA in the microbial shikimate pathway (Barker and Frost 2001; Krömer et al. 2013; Meijnen et al. 2011; Suzanne et al. 2010; Verhoef et al. 2007).

In the last two decades, shikimate pathway has been intensively studied for the biosynthesis of aromatic amino acids (L-tryptophan, L-phenylalanine, and L-tyrosine), quinones, folates, and secondary metabolites including many commercially valuable compounds (Chen et al. 2014; Curran et al. 2013; Huang et al. 2011; Jin et al. 2015; Krömer et al. 2013; Li et al. 2010; Noda et al. 2017; Weber et al. 2012) (Fig. 1). The shikimate pathway links carbohydrate metabolism to aromatic compound biosynthesis by converting phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate (E4P) from the central carbon metabolism (CCM) into 3-deoxy-d-arabino-heptulosonate-7-phosphate (DAHP). After a series of seven catalytic reactions, DHAP is transformed to chorismate, a universal precursor for commercially valuable compounds (Hu et al. 2017; Jin et al. 2015; Liu et al. 2016; Shen et al. 2017b). It is reported that improving the metabolic flux in shikimate pathway would increase the downstream target compounds titer (Bongaerts et al. 2001; Liu et al. 2016). Jung et al. (2016) reported the engineering of natural shikimate pathway and resulted in 99% conversion of *p*-coumaric acid (*p*CA) into 4-HBA. Simialry, Meijnen et al. (2011) constructed a pathway for the co-utilization of xylose and other carbon sources and considerably improved the 4-HBA yield. On the other hand, the growth and metabolism of many microorganisms can be inhibited by species-specific concentrations of 4-

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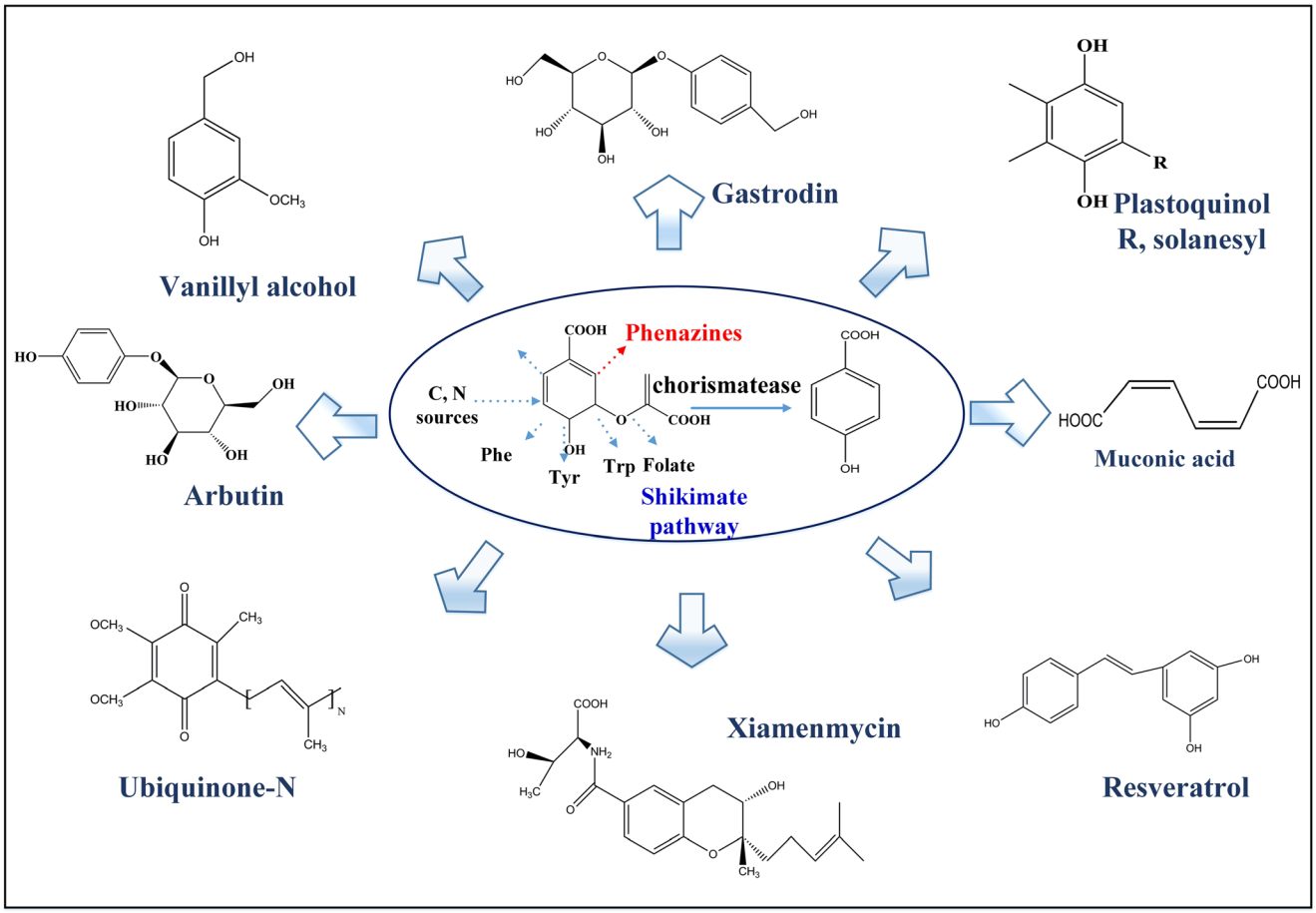

Fig. 1 4-Hydroxybenzoic acid derivatives synthesized through metabolic engineering of the shikimate pathway. Phenazines studied in our lab including phenazine-1-carboxylic acid, phenazine-1-carboxamide, 2-hydroxyphenazine, and 2-hydroxyphenazine-1-carboxylic acid

HBA (Cho et al. 1998). The higher concentrations of 4-HBA have shown toxic effects to *Escherichia coli* (Barker and Frost 2001), and *Burkholderia glumae* (Jung et al. 2016).

In prokaryotes, 4-HBA forms from chorismate via shikimate pathway. As a useful industrial platform chemical, the high titer of 4-HBA can be converted into more useful compounds like resveratrol (Kallscheuer et al. 2017), muconic acid (Sengupta et al. 2015a), gastrodin (Bai et al. 2016), xiamenmycin (Yang et al. 2014), ubiquinone (Lee et al. 2017), vanillyl alcohol (Chen et al. 2017b), and many others (Chen et al. 2017a; Pfaff et al. 2014; Shen et al. 2017a; Su et al. 2017; Yang et al. 2017) (Fig. 1). The 4-HBA-derived natural products are a large group of secondary metabolites which exhibit a wide variety of biological and pharmaceutical activities. This review describes the contemporary knowledge of the renewable and sustainable biosynthesis of 4-HBA-derived natural products using metabolic engineering and synthetic biology approaches.

Resveratrol biosynthesis

Resveratrol is a non-flavonoid polyphenolic compound with a stilbene structure and considered to be a plant antitoxin. It possesses a wide variety of biological and pharmacological activities, such as antibacterial, antioxidant, anticancer, prevention of coronary artery disease (CAD), hypolipidemic, and antimutagenic effects (Gilbert 2001; Manach et al. 2004; Spatafora and Tringali 2012; Tissier et al. 2014). Due to enormous health-promoting attributes of plant polyphenols, *E. coli* and *Saccharomyces cerevisiae* strains were metabolically engineered for enhanced biosynthesis of monolignols, stilbenes, and (2S)-flavanones (Koopman et al. 2012; Lim et al. 2011; Summerenwesenhagen and Marienhagen 2015). In recent years, stilbene and (2S)-flavanones have been successfully produced in a well-known platform organism *Corynebacterium glutamicum* (Kallscheuer et al., 2016a, b). (Kallscheuer et al. 2017) a β-oxidative phenylpropanoid degradation was designed and constructed based non-natural pathway for the synthesis of phenylpropanoid CoA thioesters starting from cheap benzoic acids as illustrated in Fig. 2. Functionally reversing the β-oxidation cycle, anabolic direction started from 4-HBA, where 4-HBA CoA-ligase (HbcL1, EbA5368) converts 4-HBA to 4-HBA-CoA in the synthetic pathway (Kallscheuer et al. 2017). The thermodynamic Gibbs free energy valus ($\Delta G^{0'}$) of the complete synthetic pathway

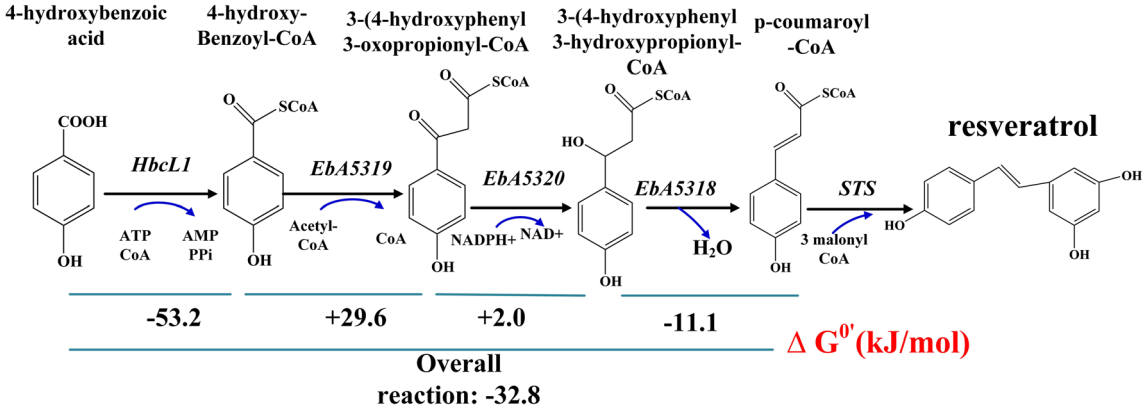

Fig. 2 Synthetic reverse β-oxidation pathway for the synthesis of resveratrol from 4-hydroxybenzoate (Kallscheuer et al. 2017) *HbcL1*: 4-hydroxybenzoate: CoA ligase, *EbA5319*: β-ketothiolase, *EbA5320*:3-hydroxy acyl-CoA dehydrogenase, *EbA5318*: enoyl-CoA hydratase, STS: stilbene synthase

was recorded to be − 32.8 kJ/mol, which indicates the feasibility of the synthetic pathway. Results demonstrated that doubling the concentration of precursor 4-HBA from 5 to 10 mM had no positive effects on the final product titer (5 mg/L). However, no resveratrol production was noted without 4-HBA supplementation, indicating that the microbial production of resveratrol can be achieved byβ-oxidative pathway starting from 4-HBA.

Muconic acid biosynthesis

Adipic acid is an important industrial dicarboxylic acid used for the manufacturing of plastics and nylon. The worldwide demand for adipic acid reached to two million tons per year (Weber et al. 2012). But its chemical production methods represent the drawbacks of non-renewability and environmental pollution, and biosynthesis of adipic acid using biorenewable feedstocks is a hopeful way. Notably, adipic acid can be easily prepared by hydrogenation of muconic acid (MA) which is a naturally occurring intermediate in the degradation process of a great variety of aromatics. At contemporary, much research efforts have been devoted to developing biotechnological processes for MA biosynthesis. Many advancements have been made in constructing microbial cell factories by engineering of non-natural biosynthetic pathways and optimizations of regulatory networks (Xie et al. 2014). Several recent reviews have comprehensively covered the detailed mechanisms of MA biosynthesis. Table 1 enlists the summary of earlier studies on the microbial-based biosynthesis of MA. Draths and Frost (1994) first reported an approach to introduce exogenous pathways in *E. coli* to achieve the MA production from glucose. In their study, a 3-dehydroshikimate acid (*DHS*) dehydratase, a protocatechuic acid decarboxylase (*PDC*) from *Klebsberg* and a catechol 1,2-dioxygenase (*CDO*) from *Acinetobacter baylyi* were co-expressed to produce MA (2.4 g/L). Similarly, Zhang et al. (2015) designed a microbial consortium to express different pathways in *E. coli*-*E. coli* co-culture system and successfully achieved MA productivity of 0.35 g/g from a glucose/xylose mixed fermentation medium. This co-culture strategy was also utilized to convert several other sugar mixtures to 4-HBA (Zhang et al. 2015). In another study, Sun et al. (2013) constructed a novel artificial pathway for the production of MA in the tryptophan biosynthesis branch, where anthranilate was converted to MA by anthranilate 1,2-dioxygenase (ADO) and CDO. Consequently, the engineered *E. coli* strain produced 389.96 mg/L MA from simple carbon sources in shake-flask experiments. The same research group established another MA biosynthesis pathway in *E. coli*, via extending shikimate pathway by introducing the hybrid SA biosynthesis pathway with its partial degradation pathway. Systematic optimization facilitated the biosynthesis of 1.5 g/L MA in the shake flasks-based batch fermentation (Lin et al. 2014). An artificial metabolic pathway was incorporated in *E. coli* by Sengupta et al. (2015a) for the biosynthesis of MA using glucose as a sole carbon source. The proposed pathway led to an efficient conversion of chorismate from the aromatic amino acid pathway to MA via 4-HBA (Fig. 3). Three enzymes, 4-HBA hydro-lyase (*pobA*), protocatechuate decarboxylase (*aroY*), and catechol 1,2-dioxygenase (*catA*) were overexpressed in *E. coli* to constitute the MA biosynthesis pathway (Sengupta et al. 2015b). In this report, using 4-HBA as essential intermediates branching out from chorismate in the shikimate pathway, MA production using the proposed pathway was promoted by exploiting almost all the 4-HBA. However, the chorismate lyase is feedback inhibited by 4-HBA (Siebert et al. 1994) and overexpression of *ubic* may increase the production of MA by converting 4-HBA to MA. It is particularly fascinating to use 4-HBA from lignin depolymerization as an additional carbon source

Table 1 Metabolic strategies and engineered microorganisms for MA production

Strain	Main precursor	MA generating enzyme	Other metabolic alterations[a]	MA titer	Fermentative process	Reference
E. coli	DHS	*ShiA+aroZ+aroY+catA*	A: *ShiA* B: *YdiB*, *aroE*, *aroG*, *ppsA*	4 g/L	Fed-batch	Zhang et al. (2015)
	Salicylic	*SMO+CDO*	A: *ppsA*, *tktA*, *aroG*, *aroL*, B: *pheA*, *tyrA*	1.5 g/L	Shake flask	Lin et al. (2014)
	Anthranilate	*trpEG+ADO+CDO*	A: $trpEG^{fbr}$, *aroE*, *aroB*, *aroL*, *ppsA*,*tktA*, $aroG^{fbr}$ B: *trpD*,	389.96 mg/L	Shake flask	Sun et al. (2013)
	4-HBA	*pobA+aroY+catA*	A: *ubic*, *aroE*, $aroF^{fbr}$, *aroL* B: *ptsH*, *ptsI*, *crr*, *pykF*	170 mg/L	Shake flask	Sengupta et al. (2015b)
	DHS	*aroZ+aroY+catA*	B: *aroE*	59.2 g/L	Fed-batch	Bui et al. (2014)
S. cerevisiae	DHS	*aroZ+aroY+catA*	A: *aroB*, *aroD*, B: *aroE*	1.5 mg/L	Shake flask	Weber et al. (2012)
	DHS	*aroZ+aroY+catA*	A: $aro4^{fbr}$, *tkt1* B: *aro3*, *zwf1*	141 mg/L	Shake flask	Curran et al. (2013)
P. putida	Benzoic acid			32 g/L	DO-start fed-batch	Bang and Choi (1995)

[a]Metabolic alterations summarized in this table do not include every specific detail, only the ones concerned in this review

A: specific gene overexpression; B: specific gene deletion

MA generating enzyme: ShiA, 12-helix transmembrane permease; AroZ, 3-dehydroshikimate dehydratase; AroY, protocatechuic acid decarboxylase; CatA, catechol 1,2-dioxygenase; SMO, salicylate 1-monooxygenase; CDO, catechol 1,2-dioxygenase; trpEG, anthranilate synthase; ADO, anthranilate 1,2-dioxygenase; *pobA*, 4-hydroxybenzoate 3-monooxygenase

accompanied by glucose (Sengupta et al. 2015a). Recently, almost doubled MA production (more than 3.1 g/L) was achieved by co-expressing "4-HBA-MA" and "DHS-MA" pathway in parallel to create a synthetic metabolic funnel (Thompson et al. 2017).

Gastrodin biosynthesis

Gastrodin is a major and active ingredient of gastrodiaelata B1, a well-known Chinese medicine commonly used in China as a sedative, anticonvulsant, antiaging, anti-inflammatory, and antimyocardial ischemia. It also enhances the immune and other vital health-related functions (Hsieh et al. 2001; Wang et al. 2007; Zhou 1991). Currently, the synthesis of gastrodin is primarily based on chemical routes and plant-based extraction processes (Wang et al. 2007; Zhou 1991), which display many disadvantages. In recent years, an array of economically important plant-based natural products including terpenoids (Ajikumar et al. 2010; Ro et al. 2006), alkaloids (Nakagawa et al. 2011; Thodey et al. 2014), and many other high value-added compounds have been reported to be synthesized by recombinant microorganisms. Bai et al. (2016) developed an artificial pathway and managed to achieve a noticeable gastrodin titer of 545 mg/L in 48 h by the engineered strain (Fig. 4).

The biosynthesis of gastrodin has also been investigated by 4-HBA precursor feeding experiments as well as genetic and biochemical approaches. A carboxylic acid reductase (*CAR*) from *Nocardai iowensis* (He et al. 2004), endogenous alcohol dehydrogenases (*ADHs*) (Bai et al. 2014) of *E. coli*, and a *Rhodiola UGT73B6* catalyzed the formation of gastrodin from 4-HBA. To further enhance the 4-HBA production, *ubic* was overexpressed to catalyze the conversion of chorismate to 4-HBA. The metabolic flux to the shikimate pathway was substantially increased through the overexpression of $aroG^{fbr}$ and *ppsA*, and the combined expression of *ubic*, $aroG^{fbs}$, and *ppsA*, potentially enhanced the biosynthesis of 4-hydroxybenzyl alcohol, then 4-hydroxybenzyl alcohol was converted to gastrodin at 545 mg/L by directed evolution of *UGT73B6*.

Xiamenmycin biosynthesis

Xiamenmycin is a prenylated benzopyran derivative (Yang et al. 2014), with remarkable anti-inflammatory activities accompanied by the anticontractile capacity of lung fibroblasts, attenuated hypertrophic scar formation and treating fibrotic diseases (Xu et al. 2012). L-threonine, 4-HBA, and a geranyl group are the three main components that constitute the xiamenmycin. The xiamenmycin biosynthetic gene cluster from *Streptomyces xiamenensis* 318 consists of five genes starting from 4-HBA (Yang et al. 2014). Feeding experiments with 4-HBA precursors confirmed that the 4-HBA acts as a

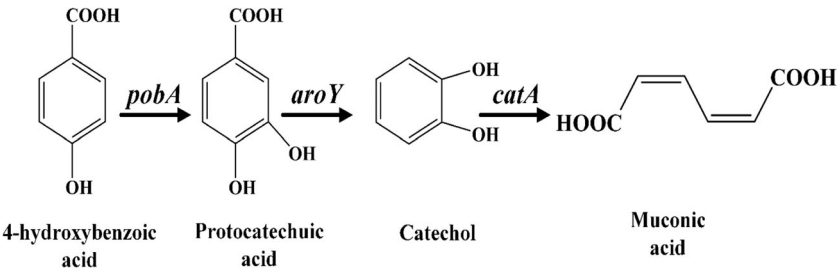

Fig. 3 Biosynthetic pathway for muconic acid (Sengupta et al. 2015a). PobA: 4-hydroxybenzoic acid hydro-lyase; AroY: protocatechuic acid decarboxylase; CatA: catechol 1,2-dioxygenase

starting unit for xiamenmycin biosynthesis. It can be seen from Fig. 5 that *XimC* (chorismatease) is responsible for the generation of 4-HBA. The *XimB* gene catalyzes 4-HBA and geranyl diphosphate (GPP) to produce 3-geranyl-4-hydroxybenzoic acid which was proposed to involve in assembly by XimB from 4-HBA starting unit and PPO extender units, then *XimD*, *XimE*, and *XimA* catalyze sequentially to form xiamenmycin (Yang et al. 2014). The function of *XimC* is to produce 4-HBA, when targeted inactivation of *XimC*, no xiamenmycin was produced, and the supplementation of 4-HBA by feeding restored the xiamenmycin production. This indicated that *XimC*, as the key switch point, might be a chorismate lyase, catalyzing chorismate to generate 4-HBA as the initial step of xiamenmycin production.

Ubiquinone biosynthesis

Coenzyme Q, commonly known as ubiquinone, plays a vital role in the electron transport chain. It is also related to many types of metabolic diseases, such as neuropathies and muscular disorders (Mancuso et al. 2010; Sharma et al. 2016). The number of isoprenyl units makes different types of coenzyme Q such as CoQ6 in *Saccharomyces cerevisiae*, CoQ8 in *E. coli*, CoQ9 in *Arabidopsos thaliana*, and CoQ10 in human and *Schizosaccharomyces cerevisiae spome* (Kawamukai 2015). In recent years, CoQ10 attracted a noticeable researchers attention due to its enormous significance in biomedical and health perspectives (Lee et al. 2017). Therefore, different strategies have been envisioned to scale up the production of CoQ. To date, industrial production of CoQ10 mainly focuses on animal tissue extraction, semi-chemical and microbial fermentation (De and Lee 2014; Kawamukai 2002). Notably, tissue extraction and chemical-based methods are high energy consumption process to produce CoQ10, and very difficult to separate optical isomers in chemical synthesis (Jing et al. 2011) which makes microbial synthesis of CoQ10 to be a preferred avenue. CoQ biosynthesis involves discrete synthetic stages including producing aromatic group to form quinone head, production of the isoprene tail, attachment of the quinone head to the isoprene tail, and the subsequent steps that culminate in the formation of the final CoQ10 product (Jeya et al. 2010; Kawamukai 2015). Both in eukaryotes and prokaryotes, 4-HBA acts as the quinone head synthesized in shikimate pathway (Fig. 6). In prokaryotes, 4-HBA is derived from chorismate, and the CoQ biosynthetic pathway in *E. coli* consists of nine enzymes, including *ubiA*, *ubiB*, *ubiC*, *ubiD*, *ubiE*, *ubiF*, *ubiG*, *ubiH*, and *IspB* (Gonzálezmariscal et al. 2014), while in eukaryotes, 4-HBA is derived from tyrosine. 4-HBA enters the CoQ biosynthetic pathway via the prenylation of the position 3 catalyzed by *Coq2* in eukaryotes or *ubiA* in bacteria, and then yields 3-polyprenyl-4-hydroxybenzoic acid for further metabolism to CoQ (Pierrel 2017). The introduction of decaprenyl diphosphate synthase gene (*ddsA*) in *E. coli* along with supplementation of 4-HBA led to improved CoQ yield and dry cell weight (DCW) (Zahiri et al. 2006). Accordingly, 4-acetylantroquinonol B (4-AAQB) can inhibit the propagation of hepatocellular carcinoma cells *HepG2* with an IC_{50} of 0.1 g/mL (Lin et al. 2010). Recently, Lin et al. (2010) reported that 4-AAQB was synthesized based on CoQ biosynthetic pathway, where the benzoquinone ring

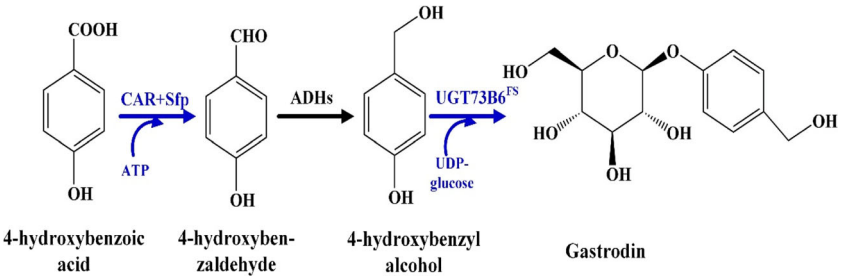

Fig. 4 Proposed biosynthetic pathway of gastrodin (Bai et al. 2016). CAR: carboxylic acid reductase; ADHs, alcohol dehydrogenase; UGT73B6FS: uridine sugar glycosyltransferase

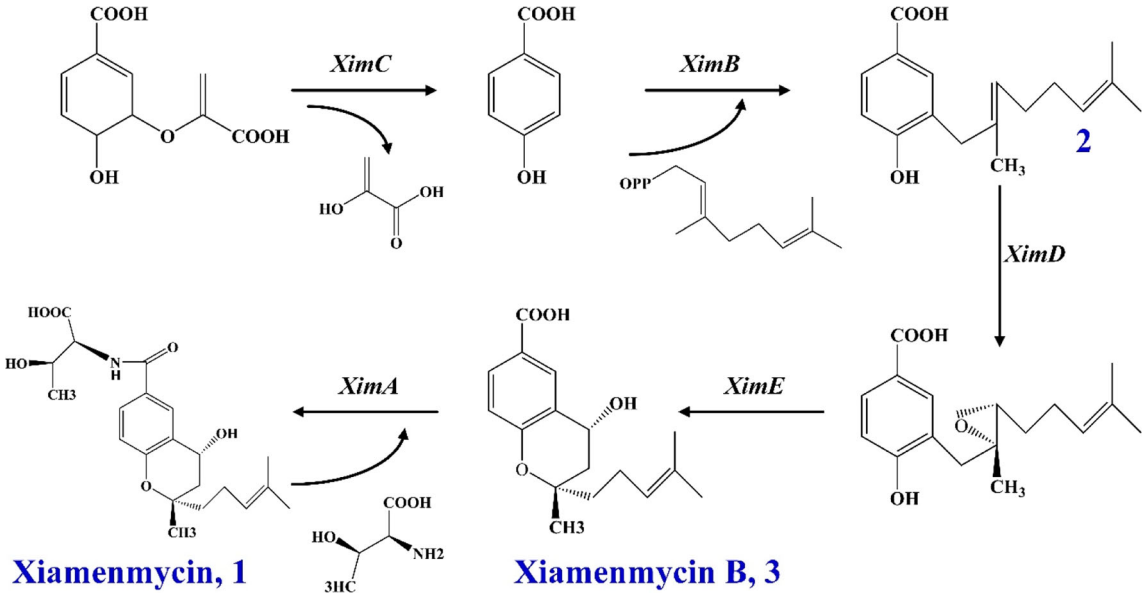

Fig. 5 Proposed biosynthetic pathway for xiamenmycin (Yang et al. 2014). XimA: amide synthetase; XimB: 4-hydroxybenzoate geranyl transferase; XimC: chorismate lyase; XimD: epoxidase; XimE: SnoaL-like cyclase

might be originated from shikimate pathway. The 4-HBA addition substantially improved the production of 4-AAQB. The biosynthesis pathway of CoQ and 4-AAQB was assumed to be closely related and 4-AAQB might be a metabolic product of CoQ in the same pathway (Yang et al. 2017). In *Xanthomonas campestris pv. campestris* (*Xcc*), *XanB2* is a unique bifunctional chorismatase, which is the alternative source of 4-HBA for CoQ8 biosynthesis. When *XanB2* was deleted in *Xcc*, the derivative was deficient for CoQ biosynthesis and 4-HBA production decreased (Zhou et al. 2013). When the supplementation and availability of 4-HBA in *Rhodobacter sphaeroides* were increased by heterologous

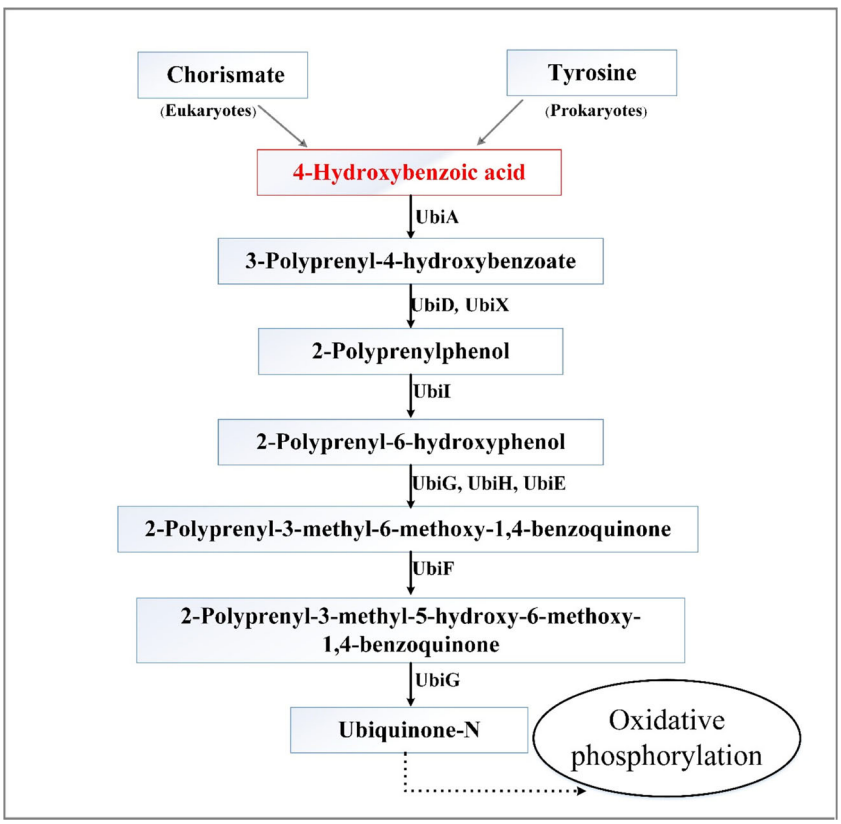

Fig. 6 Biosynthesis of coenzyme Q10 from 4-hydroxybenzoic acid. UbiA: 4-hydroxybenzoate polyprenyltransferase; UbiD: 4-hydroxy-3-polyprenylbenzoate decarboxylase; UbiE: demethylmenaquinone methyltransferase; UbiF: 2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinol hydroxylase; UbiG: 2-polyprenyl-6-hydroxyphenyl methylase; UbiH: 2-octaprenyl-6-methoxyphenol hydroxylase; UbiI: 2-octaprenylphenol hydroxylase; UbiX: 4-hydroxy-3-polyprenylbenzoate decarboxylase

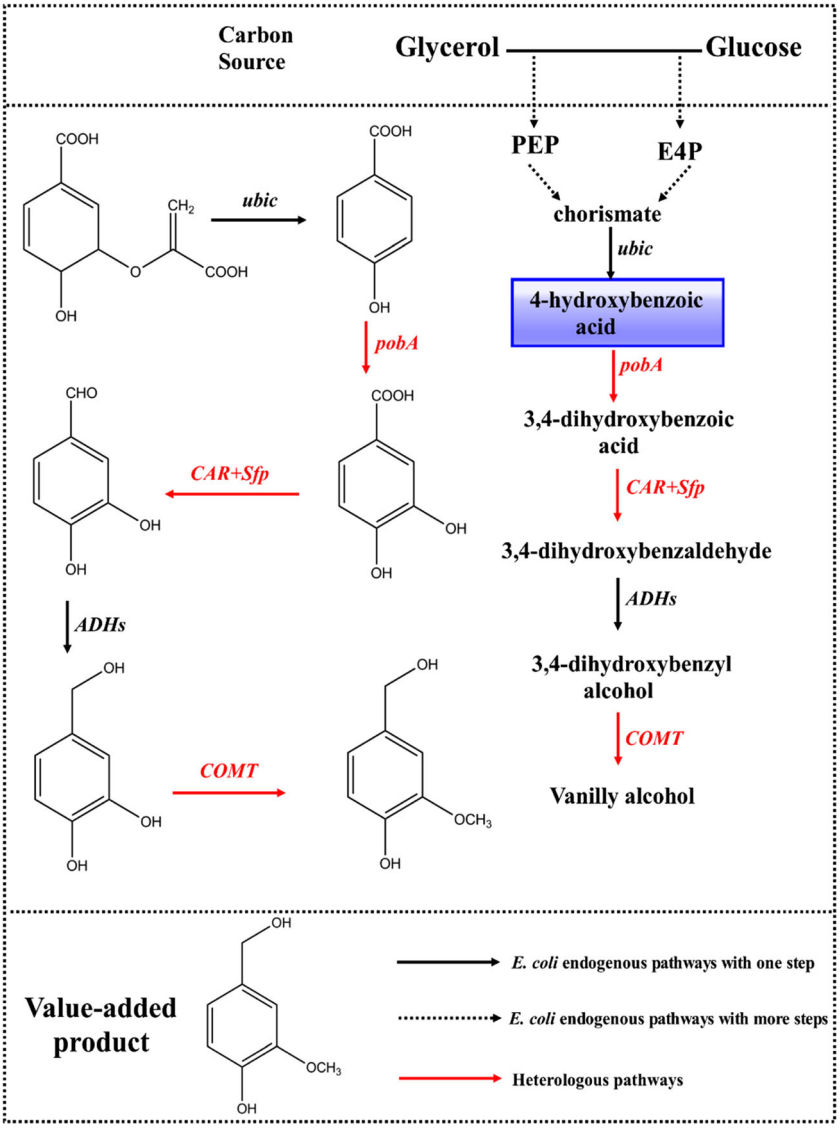

Fig. 7 Novel biosynthetic pathway of vanillyl alcohol (Chen et al. 2017b). Ubic: chorismate lyase; PobA: 4-hydroxybenzoate 3-monooxygenase; CAR+Sfp: carboxylic acid reductase; COMT: caffeate O-methyltransferase; *ADHs*: alcohol dehydrogenase

expression of three membrane transport protein, the CoQ10 productivity was substantially improved by enhancing the uptake of extracellular 4-HBA and addition of external 4-HBA, reaching maximum of 18.06 mg/g DCW (Qi et al. 2017).

Vanillyl alcohol biosynthesis

Vanillyl alcohol is an edible spice for all kinds of food, cosmetics, pharmaceutical, and chemicals. Until now, the leading route for vanilly alcohol production is direct extraction from a variety of plants; however, these methods display several drawbacks, such as the limited supply of raw materials, strict reaction conditions, and low productivities. Therefore, the eco-friendlier microbial synthesis can be an attractive alternative to vanillyl alcohol production. Some reports have introduced the biosynthesis of vanillin which is the precursor of vanillyl alcohol (Brochado et al. 2010; Hansen et al. 2015). A unique non-natural pathway for the biosynthesis of vanillyl alcohol from 4-HBA has been illustrated in Fig. 7 utilizing three heterologous enzymes, namely 4-hydroxybenzoate hydroxylase (PobA), carboxylic acid reductase (*CAR*), and caffeate *O*-methyltransferase (*COMT*) (Chen et al. 2017b). In this work, 4-HBA generated from shikimate is converted to 3,4-dihydroxybenzoic acid catalyzed by 4-hydroxybenzoate 3-monooxygenase PobA from *Pseudomonas aeruginosa*. Afterwards, the resulting product was catalyzed by carboxylic acid reductase *CAR*, phosphopantetheinyl transferase *ADHs*, and O-methyltransferase *COMT* to produce vanillyl alcohol. For the purpose of enhancing chorismate conversion into 4-HBA, one chorismate lyase *ubic* was overexpressed, which reveals that more 4-HBA is beneficial for producing target products. To further increase the metabolic flux for shikimate precursors, *aroL*, *ppsA*, *tktA*, and $aroG^{fbr}$ were overexpressed,

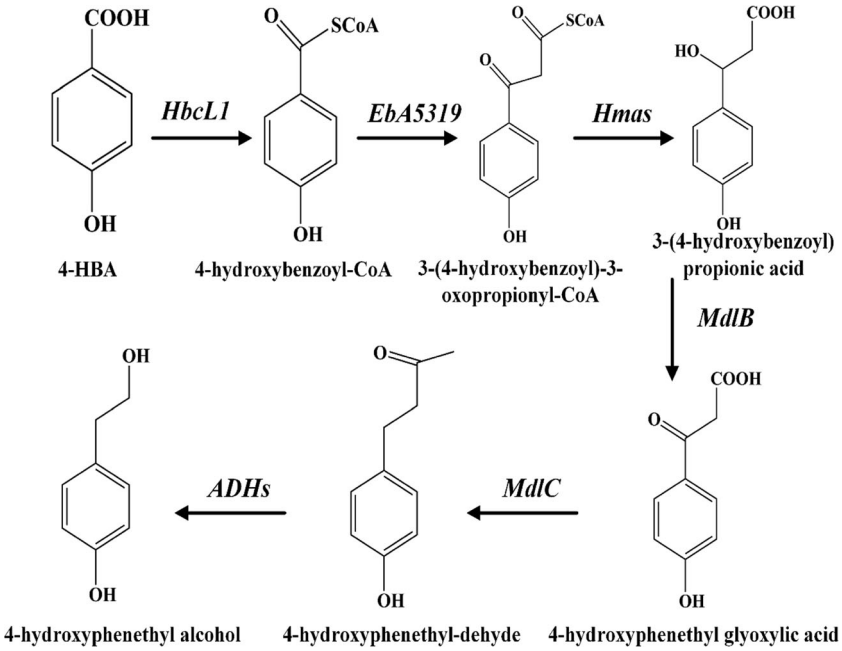

Fig. 8 A schematic representation of 4-hydroxyphenyl alcohol produced by 4-hydroxybenzoic acid; *HbcL1*: 4-hydroxybenzoate: CoA ligase; *EbA5319*: β-ketothiolase *Hmas*: 3-(4-hydroxy benzoyl) propionic acid synthase; *MdlB*: (S)-propionic acid dehydrogenase; *MdlC*: phenethyl glyoxylic acid decarboxylase; *ADH*: alcohol dehydrogenase

and resultantly 240.69 mg/L vanillyl alcohol was achieved via modular optimization.

Concluding remarks and future perspectives

4-HBA is a bulk chemical due to its wide-ranging applications for the biosynthesis of numerous value-added products with various biological functions. Insight into 4-HBA derivatives biosynthesis accelerated rapidly with the development of molecular biology and genetic techniques. Recently concerted research efforts have been made in developing biotechnological routes to produce 4-HBA derivatives, and several research groups have reported the engineered strains for 4-HBA derivatives production, making significant progress with respect to both yields and concentrations. Further, the engineering of novel pathways together with a mixed-substrate feeding strategy might be conceived to improve the 4-HBA yield.

As shown in Fig. 8, 4-hydroxyphenyl alcohol could be synthesized from 4-HBA, which is mainly used for the synthesis of cardiovascular drugs metoprolol. There is still a wide range of genetically and biochemically uncharacterized 4-HBA derivatives requiring more efforts to uncover the fine-natural products. Biotechnology has expanded the range of compounds produced and the type of organism used as a biological chassis; more enzymes such as prenyltransferase and glycosyltransferase will be modified to yield 4-HBA. In recent years, it has been witnessed to biosynthesize innumerable natural products using 4-HBA as precursors. Many programmable 4-HBA oligomers can be synthesized through regioselective reactions or 4-HBA tetramers which can be synthesized via a stereo convergent radical equilibrium like resveratrol.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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