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Review

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Current Status of Microbial Phenylethanoid Biosynthesis

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Phenylethanoids, including 2-phenylethanol, tyrosol, and salidroside are a group of phenolic compounds with a C6-C2 carbon skeleton synthesized by plants. Phenylethanoids display a variety of biological activities, including antibacterial, anticancer, anti-inflammatory, neuroprotective, and anti-asthmatic activities. Recently, successful microbial synthesis of phenylethanoids through metabolic engineering and synthetic biology approaches has been reported and could allow phenylethanoid production from alternative microbial sources. Here, we review the recent achievements in the synthesis of phenylethanoids by microorganisms. The work done so far will contribute to the production of diverse phenylethanoids using various microbial systems and facilitate exploration of further diverse biological activities of phenylethanoids.

Keywords: Metabolic engineering, microbial production, phenylethanoids

Plants synthesize a variety of phenolic compounds via the phenylpropanoid pathway, which is a pathway unique to plants [1]. These phenolic compounds found in nature can be classified based on the backbone of their carbon skeleton (Table 1). Phenolic acid, whose carbon skeleton is benzoic acid derivatives (C6-C1), phenylethanoid (C6-C2), phenylpropanoid (C6-C3), stilbene (C6-C2-C6), and flavonoid (C6-C3-C6) are major groups [2].

Diverse phenolic compounds are being widely used in our current life. Some of them are building blocks for polymer synthesis [3], some are used as ingredients in food [4], and some of them are considered bioactive compounds that have potential for the development of new medicines [5]. The antioxidant activity of phenolic compounds is conspicuous, but additional biological activities have been revealed using extracts from diverse plants. These include anticancer, anti-inflammatory, antibacterial, antiviral, antifungal, anticoagulant, and antihypertensive activities [6–9].

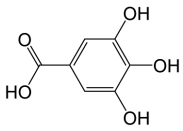
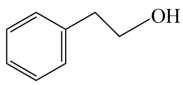
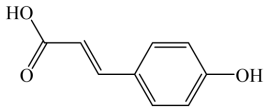
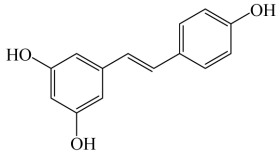
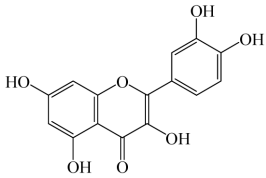
The phenylpropanoid pathway, which uses amino acids phenylalanine or tyrosine, leads to the synthesis of diverse phenolic compounds. Genes involved in phenolic compounds biosynthesis have been cloned and characterized from model plants such as *Arabidopsis thaliana* and *Oryza sativa* to medicinal plants [1]. These genes have been expressed in microorganisms to produce value-added phenolic compounds.

Among the phenolic compounds, phenylethanoids, which have a C6-C2 carbon skeleton, and the biological pathway for phenylethanoid synthesis is beginning to be elucidated. In this review, we focus on the recent developments in phenylethanoid biosynthesis using engineered microorganisms.

Classification and Biological Activities of Phenylethanoids

Phenylethanoids have a phenethyl alcohol structure and 2-phenylethanol (2-PE), tyrosol, and hydroxytyrosol are typical examples of phenylethanoids. Phenylethanoids may be conjugated with glycosides and hydroxycinnamoic acids (HCs) in limited plant families [9, 10]. Phenylethanoid glycosides are found in various medicinal plants and more than 300 new phenylethanoid glycosides have been identified in the last twenty years [9, 10]. Synthesis of phenylethanoid glycosides is not well investigated. Salidroside (2-(4-hydroxyphenyl) ethyl β-D-glucopyranoside), one of the phenylethanoid glycosides found in the medicinal plant *Rhodiolarosea* is a tyrosol glucoside and is thought display antidepressant and anxiolytic activities [11]. 2-PE forms an ester conjugate with caffeic acid called CAPE

Table 1. Classification of phenolic compounds.

Classification	Example	Typical structure
Phenolic acid (C6-C1 backbone)	4-Hydroxybenzoic acid Gallic acid Salicylic acid	
Phenylethanoid (C6-C2 backbone)	2-Phenylethanol Tyrosol Salidroside	
Hydroxycinnamate (C6-C3 backbone)	*p*-Coumaric acid Coumarin Chlorogenic acid	
Stilbenoid (C6-C2-C6 backbone)	Resveratrol Piceathannol Pallidol	
Flavonoid (C6-C3-C6 backbone)	Quercetin Genistein Apigenin	

(caffeic acid phenethyl ester), which is one of constituents of propolis [12].

2-PE is a flavor compound that is widely used in the cosmetic and food industries. Plants are the major source of 2-PE and there are some limitations to supply the demands from market. Tyrosol and hydroxytyrosol are major ingredients of olive oil and are known antioxidants [13]. Both compounds show neuroprotective activity against amyloid β formation and therefore help prevent Alzheimer's disease [14] and release neuropathy [15]. These two compounds were known to prevent atherosclerosis and cancer, and display anti-inflammatory activities [16]. Therefore, they have potential uses in cardiovascular diseases, cancer, and AIDS [17]. Salidroside confers protection from brain cell damage [18] and bone loss [19] and reduces the side effects of chemotherapy [20].

CAPE is known to possess various biological activities including anticancer, antimicrobial, antioxidant, and anti-inflammatory activities [21, 22]. CAPE also shows anti-asthmatic activity and inhibits 5-lipoxygenase and leukotriene biosynthesis more effectively than the clinically-approved Zileuton [23]. CAPE or its derivatives have been synthesized chemically [24–26]. The caffeic acid moiety and/or phenylethanol moiety of CAPE were changed and 19 derivatives were synthesized [25]. Some of these derivatives showed better cytoprotective or neuritogenic activities than CAPE. These CAPE derivatives showed diverse activities including anti-cancer, anti-inflammatory, and immunomodulatory activities [25].

Phenylethanoid Synthesis in Microorganisms

Biological synthesis of phenylethanoids has been studied and 2-PE and tyrosol are known to be synthesized from phenylalanine and tyrosine, respectively (Fig. 1). In *Saccharomyces cerevisiae*, three genes (*Aro9*, *Aro10*, and *Adh2*), all of which are part of the Ehrlich pathway [27], are involved in the synthesis of 2-PE from phenylalanine. Phenylalanine deaminase (Aro9) modifies phenylalanine to form phenylpyruvate, and phenylpyruvate decarboxylase (Aro10) catalyzes conversion of phenylpyruvate to phenylacetaldehyde, which is reversibly converted into 2-phenylethanol by alcohol dehydrogenase (Adh2) (Fig. 1A) [28]. In plants, there are two putative pathways for tyrosol synthesis (Fig. 1B). The first pathway is mediated by two enzymes, an aromatic amino acid decarboxylase such as phenylalanine decarboxylase (PDC) and tyrosine decarboxylase (TDC), and a monoamine oxidase such as phenethylamine

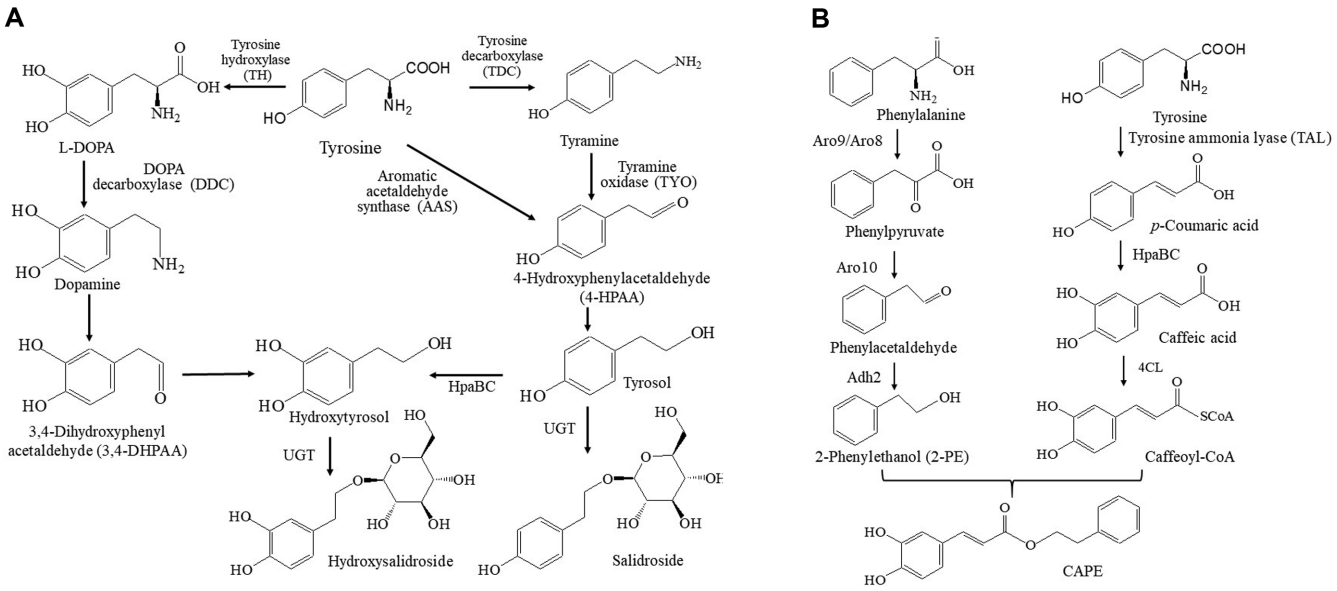


Fig. 1. (**A**) Synthesis of tyrosol, hydroxytyrosol, salidroside, and hydroxysalidroside from tyrosine. Tyrosine can be converted to 4-HPAA by either TDC and TYO or AAS, which leads to the synthesis of four phenylethanoids. Tyrosine can be hydroxylated by TH to form DOPA, which is converted to hydroxytyrosol. (**B**) Synthesis of CAPE from phenylalanine and tyrosine. 2-PE is synthesized from phenylalanine by Aro9, Aro10, and ADHs and Caffeoyl-CoA is synthesized from tyrosine by TAL, HpaBC, and 4CL. 2-PE and cafferoyl-CoA are conjugated to form CAPE.

oxidase (PEO) and tyramine oxidase (TYO) [29]. Combination of these two genes could lead to the synthesis of phenylethanol and tyrosol from phenylalanine and tyrosine, respectively. The second pathway is mediated by a bifunctional enzyme called aromatic amino acid decarboxylase (AAS) which catalyzes both decarboxylation and oxidation [30, 31].

Microbial systems have been used to synthesize phenylethanoids; for instance, 2-PE was synthesized using various microorganisms. However, 2-PE inhibits microbial growth at a concentration of 2–3 g/l [33], which limits the use of microorganisms for 2-PE synthesis. Some yeast strains like *Pichia fermentans*are known to synthesize 2-PE naturally [34]. By optimization of the medium for *P. fermentans*, 3.71 mM 2-PE was reported to be synthesized [25]. *S. cerevisiae* and *Kiuyveromyces marxianus* are typical yeast systems that have been engineered to synthesize increases amounts of 2-PE. Both *S. cerevisiae* and *K. marxianus* share the decarboxylase Aro10 that converts phenylpyruvate into phenylacetaldehyde [28, 36]. Phenylalanine was used as a starting material for *S. cerevisiae* whereas phenylpyruvate was used for *K. marxianus* (Table 2). In *S. cerevisiae*, *Aro9* and *Aro10*, both of which encode key enzymes for the conversion of phenylalanine into phenylacetaldehyde, were overexpressed along with *Aro80* (a transcription activator of *Aro9* and *Aro10*), and *Ald3* which encodes aldehyde dehydrogenase, was deleted in order to prevent the conversion of phenylacetaldehyde into phenylacetate. After optimization of the fermentation conditions, 49.93 mM 2-PE was synthesized in *S. cerevisiae* [36]. In *K. marxianus* *Aro10* and *Adh2* (alcohol dehydrogenase) were overexpressed. In addition, $aroG^{fbr}$, which is a feedback-inhibition mutant version of *aroG* and encodes phospho-2-dehydro-3-deoxyheptonate aldolase and catalyzes the condensation of phosphoenolpyruvate (PEP) and erythrose 4-phosphate (E4P) at the first step of the shikimate pathway in *Escherichia coli*, was overexpressed to increase the phenylalanine concentration. Using these approaches, 10.64 mM 2-PE was synthesized in *K. marxianus*.

E. coli was also a good system to synthesize 2-PE and its shikimate pathway was well elucidated [37]. In order to increase the phenylalanine and tyrosine production in *E. coli*, the genes of the shikimate pathway were overexpressed or deleted. AroG and AroF function at the first step of shikimate pathway and condensate phosphoenolpyruvate and erythrose 4-phosphate to form phospho-2-dehydro-3-deoxyheptonate. Overexpression of either of these genes in *E. coli* resulted in increased phenylalanine and tyrosine production. Two genes, *ppsA* and *tktA*, involved in production of PEP and E4P, respectively, were also

Table 2. Summary of phenylethanoids production in microorganisms.

Microorganisms	Genes used	Engineering of shikimate pathway genes of *E. coli*	Substrate	Product	Yield	Reference
Saccharomyces cerevisiae	*Aro9*, *Aro10*, *Aro80* overexpression/*Ald3* deletion		Glucose + 10 g/l phenylalanine (two-phase fermentation)	2-PE	49.93 mM	[36]
Klvyeromycesm arxianus	*Aro10*, *Adh2*, *aroG* overexpression		Glucose	2-PE	10.64 mM	[28]
Escherichia coli	*Adh1*, *Kdc*, *AroF*, *pheA* overexpression		Glucose	2-PE	2.33 mM	[41]
Pichia fermentans			18% sucrose + 0.25% yeast extract + 0.1% phenylalanine	2-PE	3.71 mM	[34]
Escherichia coli	*TDC*, *TYO* overexpression	*feaB* deletion	Glucose	tyrosol	0.5 mM	[42]
Escherichia coli	*ARO10*, *ARO8* overexpression	*feaB* deletion	10 mM tyrosine	tyrosol	8.71 mM	[43]
Escherichia coli	*Aro10*	*aroG*, *tyrA*, *ppsA*, *aroE*, *aroD*, *aroB* overexpression *tyrR*, *pykA*, *pykF*, *phe A* deletion	Glucose	tyrosol	6.71 mM	[45]
Escherichia coli	*AAS* overexpression,	*TyrR*, *PheA*, *feaB* deletion	Glucose	tyrosol	3.77 mM	[44]
Escherichia coli	*PCD*, *DHPR*,*TH*, *TDC*, *TYO* overexpression	*feaB* deletion	Glucose	tyrosol	0.08 mM	[42]
Escherichia coli	*AAS*, *HpaBC* overexpression,	*TyrR*, *PheA*, *feaB* deletion	Glucose	hydroxytyrosol	1.35 mM	[44]
Escherichia coli	*TDC*, *TYO*, *HpaBC* overexpression,	*TyrR*, *PheA*, *feaB* deletion	Glucose	hydroxytyrosol	1.74 mM	[49]
Escherichia coli	*AAS*, *UGT85A1* overexpression	*TyrR*, *PheA*, *feaB* deletion	Glucose	salidroside	0.96 mM	[44]
Escherichia coli	*ARO10*, *UGT73B6* overexpression	*aroG*, *tyrA*, *ppsA*, *aroE*, *aroD*, *aroB* overexpression *tyrR*, *pykA*, *pykF*, *pheA* deletion	Glucose	salidroside	0.19 mM	[45]
Escherichia coli	$UGT_{BL}1$		7.24 mM tyrosol	saliroside/icariside	3.46 mM/ 3.30 mM	[51]
Escherichia coli	*UGT73C6* overexpression		100 μM salidroside	hydroxysalidroside	50 μM	[49]
Escherichia coli	*ATF*, *4CL*, *TAL*, *HpaBC* overexpression	*tyrA*, *ppsA*, *tktA*, *aroG* overexpression *tyrR*, *pheA*, *ydiI* deletion	Glucose	CAPE	0.21 mM	[56]

overexpressed to supply substrates for AroG and AroF. *pheA* and *tyrA* were overexpressed to convert chorismate to phenylalanine and tyrosine. In addition, *pheA* overexpression increased the production of phenylalanine whereas *tyrA* overexpression increased tyrosine production. The transcription factor TyrR was deleted because it is inhibited by phenylalanine and tyrosine in a feedback manner (Fig. 2) [38–40]. Two genes from *S. cerevisiae*, *Adh2* and *Aro10* were overexpressed in *E. coli* similar to the approach that was used in *S. cerevisiae*. Since phenylalanine is a substrate of 2-PE, two genes, *aroF* encoding phospho-2-dehydro-3-deoxyheptonate aldolase and *pheA* encoding

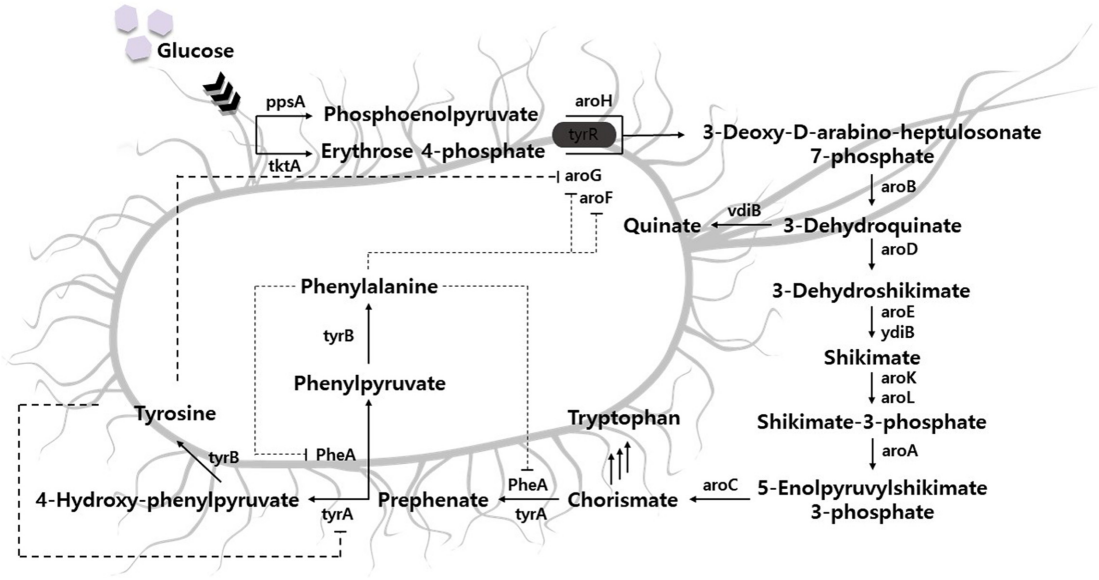


Fig. 2. Shikimic acid pathway in *Escherichia coli*.

chorismate mutase/prephenate dehydratase were also overexpressed and the final yield of 2-PE was 2.33 mM [41].

Tyrosol synthesis was mainly investigated in *E. coli*. TYO from *Micrococcus luteus* and TDC from *Papaver somniferum* were overexpressed in *E. coli* and *feaB* encoding phenylacetaldehyde dehydrogenase, which has a function similar to *ALD3* in *S. cerevisiae*, was deleted. Using this system, 0.5 mM tyrosol was synthesized [42]. In another study, *Aro8* and *Aro10* from *S. cerevisiae* were overexpressed in *E. coli* and *pheA* and *feaB* were deleted, resulting in the synthesis of 4.15 mM tyrosol upon supplying 10 mM tyrosine [43]. By introducing the bifunctional gene *AAS* into *E. coli* and engineering the *E. coli* tyrosine biosynthesis pathway to increase intracellular tyrosine concentration by deleting *tyrR* and *pheA*, 3.77 mM tyrosol was synthesized [44]. When more genes (*tyrA*, *ppsA*, *tktA*, *aroD*, and *aroB*) of the shikimate pathway of *E. coli* (Fig. 2) were overexpressed and *pykA* and *pykF*, both of which encode pyruvate kinase involved in the conversion of PEP into pyruvate, were deleted, the tyrosol production was 6.71 mM [45].

Two routes were used for the synthesis of hydroxytyrosol; the first route is through tyrosol and the second route is through dihydroxyphenylalanine (DOPA). HpaBC (hydroxyphenylacetate 3-monooxygenase) from *E. coli* could convert tyrosol into hydroxytyrol and tyrosine into DOPA (Fig. 1A) [46–48]. The overexpression of *AAS* and *HpaBC* in engineered *E. coli* resulted in 1.35 mM hydroxytyrosol production [35]. Introducing the other route using *TDC* and *TYO* along with *HpaBC* into *E. coli* resulted in 1.74 mM hydroxytyrosol production [49]. Instead of *HpaBC*, *TH* (tyrosine hydroxylase) along with *TDC* and *TYO* was overexpressed. TH uses tetrahydromonapterin (MH4) as a cofactor. To increase tyrosine hydroxylation by supplying more cofactor for TH, two genes, *PCD* encoding pterin-4a-carbinolamine dehydratase and *DHPR* encoding dihydropteridine reductase, were overexpressed. The resulting *E. coli* strain synthesized 0.08 mM hydroxytyrosol from glucose [42].

Salidroside is a typical phenylethanoid glycoside. The glycosylation of tyrosol into salidroside is catalyzed by uridine diphosphate (UDP) dependent glucosyltransferases (UGTs). Three UGTs (UGT73B6, UGT72B14, and UGT74R1) were isolated from the salidroside producing plant *Reynoutriasachalinensis* and overexpression of each of these genes in this plant resulted in increased salidroside content [29, 50]. Introduction of UGT73B6 along with the tyrosol biosynthesis genes in *E. coli* appeared to produce salidroside (0.19 mM) as well as icariside D2 (0.21 mM) [45]. This indicated that UGT73B6 is not specific for salidroside synthesis at least in *E. coli*. The recent result of tyrosol biotransformation into salidroside using *E. coli* expressing UGT from *Bacillus licheniformis* showed the production of both salidroside and icariside D2 [51]. The UGTs found so far attach glucose to both the phenolic hydroxyl group and alcoholic hydroxyl group. Chung *et al.* [44] screened *Arabidopsis thaliana* UGTs to synthesize

salidroside from tyrosol and found that AtUGT73C5, AtUGT73C6, and AtUGT85A1 specifically synthesized salidroside, and that AtUGT84A1 showed the highest production of salidroside. AtUGT84A1 also converted hydroxytyrosol into salidroside [49]. By combining the tyrosol biosynthesis pathway with *AtUGT84A1* in *E. coli*, 0.99 mM salidroside was synthesized [44].

CAPE is an ester between phenylethanol and caffeic acid. Caffeic acid is derived from tyrosine and its biosynthetic pathway in plants is well-established. Tyrosine is a starting substance and deamination of tyrosine by tyrosine ammonia lyase (TAL) leads to the synthesis of *p*-coumaric acid. Subsequent hydroxylation of *p*-coumaric acid results in caffeic acid formation [48]. The *TAL* and *hydroxylase* for *p*-coumaric acid have been cloned and characterized in plants and microorganisms [52–54]. However, the in vivo CAPE synthesis pathway is still unknown. Biological synthesis of CAPE using Novozyme 235 (a kind of lipase) has been reported. Two substrates, caffeic acid and 2-PE were mixed in the presence of Novozyme 235 to form CAPE [55]. An esterase (ATF) from *S. cerevisiae* was used to make a conjugation between caffeoyl-CoA and 2-PE to synthesize CAPE and its derivatives in engineered *E. coli* [56]. Both the 2-PE biosynthesis pathway and caffeic acid biosynthesis pathway were introduced in *E. coli*. Notably, the *E. coli ydiI* (encoding thioesterase) deletion mutant was used, in which caffeoyl-CoA reduces degradation. Thus, by using various metabolic engineering and synthetic biology approaches, approximately 0.21 mM CAPE was synthesized.

Microbial production of phenolic compounds has been studied for the last 15 years. However, the study of phenylethanoid biosynthesis has begun recently and there are many unsolved questions. More genes specific for phenylethanoids are being cloned, and the best combinations among them need to be found. In addition, fine tuning of metabolic pathways and optimization of production processes is needed to improve productivity. In the near future, these obstacles will be overcome and industrial production of some phenylethanoids using microbial systems will be feasible.

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Conflict of Interest

The authors have no financial conflicts of interest to declare.

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