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MINI-REVIEW

Recent advances in metabolic engineering of *Corynebacterium glutamicum* for bioproduction of value-added aromatic chemicals and natural products

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Abstract

Recent progress in synthetic and systems metabolic engineering technologies has explored the potential of microbial cell factories for the production of industrially relevant bulk and fine chemicals from renewable biomass resources in an eco-friendly manner. *Corynebacterium glutamicum*, a workhorse for industrial amino acid production, has currently evolved into a promising microbial platform for bioproduction of various natural and non-natural chemicals from renewable feedstocks. Notably, it has been recently demonstrated that metabolically engineered *C. glutamicum* can overproduce several commercially valuable aromatic and related chemicals such as shikimate, 4-hydroxybenzoate, and 4-aminobenzoate from sugars at remarkably high titer suitable to commercial application. On the other hand, overexpression and/or extension of its endogenous metabolic pathways by integrating heterologous metabolic pathways enabled production of structurally intricate and valuable natural chemicals like plant polyphenols, carotenoids, and fatty acids. In this review, we summarize recent advances in metabolic engineering of *C. glutamicum* for production of those value-added aromatics and other natural products, which highlights high potential and the versatility of this microbe for bioproduction of diverse chemicals.

Keywords *Corynebacterium glutamicum* · Aromatic compounds · Shikimate pathway · Plant polyphenols · Terpenoids · Metabolic engineering

Introduction

In the past few decades, along with growing concerns about environmental issues and establishing sustainable economy independent of fossil fuels, much efforts have been devoted in eco-friendly microbial production of a wide variety of fuels and commodity chemicals with industrial relevance from renewable resources (Atsumi and Liao 2008; Becker and Wittmann 2015; Choi et al. 2015a; Nielsen et al. 2013; Turner et al. 2018). An important class of diverse chemicals, biotechnological production of which has recently gained more and more attention is aromatic compounds. They serve a vast market in the chemical industry and have numerous industrial applications as the building blocks for the synthesis of polymer materials like functional plastics and fibers, food and feed additives, nutraceuticals, and pharmaceuticals (Averesch and Kromer 2018; Kromer et al. 2013). Currently, most of industrially important aromatic compounds are produced by chemical conversion from petroleum-based feedstocks (e.g., benzene, toluene, xylene), which is not sustainable and relies on the extensive use of energy and harmful solvents, resulting in large CO_2 emissions. From the environmental point of view, biotechnological production of aromatic chemicals from renewable sugar feedstocks by eco-friendly manner has received much attention as a promising alternative (Averesch and Kromer 2018; Koma et al. 2012; Lee and Wendisch 2017; Noda and Kondo 2017; Wang et al. 2017). On the other hand, target compounds of bioproduction have also expanded to diverse and structurally intricate aromatic and other natural chemicals like plant polyphenols and terpenoids, which are produced as secondary metabolites by plants and microorganisms. They exhibit various human and animal health-promoting activities and thus have possible applications in pharmaceuticals, nutraceuticals, flavors, and cosmetic

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industries (Scalbert et al. 2005b; Suastegui and Shao 2016). They are currently produced by chemical synthesis or extraction from natural plant producers, but their productivities and yields are limited. In this context, fermentative production of those valuable natural chemicals directly from abundant and inexpensive sugar feedstocks also came into focus and has been extensively studied using model microorganisms like *Escherichia coli* and *Saccharomyces cerevisiae* (Jiang and Zhang 2016; Suastegui and Shao 2016).

Corynebacterium glutamicum, a Gram-positive, non-pathogenic soil bacterium, has been historically used in the large-scale industrial production of amino acids for more than 50 years since its discovery as a glutamate-producing bacterium from a Japanese soil (Eggeling and Bott 2005; Ikeda and Takeno 2013; Kinoshita 1985; Leuchtenberger et al. 2005). This bacterium has many physiological properties advantageous for fermetative production, which include (a) vigorous sugar consumption under either aerobic or anaerobic conditions regardless of cell growth by high-density cells (Inui et al. 2004; Okino et al. 2005), (b) an innate absence of carbon catabolite repression, allowing simultaneous utilization of various sugar mixtures such as hexoses and pentoses in engineered strains (Becker and Wittmann 2012; Blombach and Seibold 2010; Sasaki et al. 2009), and (c) high tolerance to toxic alcohols and aromatic compounds (Kitade et al. 2018; Kubota et al. 2016; Liu et al. 2013b), as well as to fermentation inhibitors derived from lignocellulosic biomass pretreatment (Sakai et al. 2007). In addition, the technological advancement of genetic engineering tools (Baritugo et al. 2018; Lee et al. 2016) and omics-based global analysis technologies along with the accompanying progress in molecular biological knowledge for its metabolism and physiology enabled rational metabolic engineering of this bacterium. Extensive research efforts have been focused on metabolic engineering of *C. glutamicum* that allowed this microbe to evolve into one of the most promising microbial platforms for bioproduction of diverse chemicals beyond classical amino acids from renewable resources (Baritugo et al. 2018; Becker et al. 2018; Becker and Wittmann 2015; Becker and Wittmann 2012; Jojima et al. 2013; Lee et al. 2016). These products include biofuels (e.g., ethanol, isobutanol, and higher alcohols) (Blombach et al. 2011; Jojima et al. 2015; Siebert and Wendisch 2015; Smith et al. 2010; Xiao et al. 2016; Yamamoto et al. 2013), organic acids, and diamines for biopolymer application [e.g., lactate, succinate, putrescine (1,4-diaminobutane), and cadaverine (1,5-diaminopentane)] (Baritugo et al. 2018; Becker et al. 2018; Becker and Wittmann 2012; Jojima et al. 2013; Tsuge et al. 2015; Tsuge et al. 2016). The access of *C. glutamicum* to non-native carbon sources such as pentoses (Kawaguchi et al. 2008; Kawaguchi et al. 2006; Sasaki et al. 2009; Schneider et al. 2011) and glycerol (Meiswinkel et al. 2013; Rittmann et al. 2008) has also been extensively engineered, enabling efficient utilization of lignocellulosic feedstocks as well as a waste material in the biodiesel industry (Becker and Wittmann 2012; Buschke et al. 2013; Wendisch et al. 2016; Zahoor et al. 2012).

In addition to the above-mentioned commodity chemicals, product portfolio of *C. glutamicum* has also been recently extended to natural and non-natural value-added chemicals such as shikimate (Kogure et al. 2016), aromatic compounds like phenolic acids (Fig. 1 and Table 1) (Kallscheuer and Marienhagen 2018; Kitade et al. 2018; Kubota et al. 2016; Okai et al. 2016) as well as structurally more intricate plant polyphenols (e.g., stilbenoids and flavonoids) (Fig. 2 and Table 2) (Kallscheuer et al. 2016), carotenoids (Fig. 3 and Table 3) (Heider and Wendisch 2015), and fatty acids (Table 3) (Plassmeier et al. 2016; Takeno et al. 2013). These value-added chemicals have numerous applications in the field of high-performance biopolymers, pharmaceuticals, nutraceuticals, flavors, and cosmetics. In engineered *C. glutamicum*, these compounds can be formed in or derived from endogenous aromatics or terpenoid synthesis pathways by combining heterologous metabolic enzymes (Fig. 1, Fig. 2, and Fig. 3) (Pickens et al. 2011). In particular, recent findings that metabolically engineered *C. glutamicum* has ability to overproduce shikimate (Kogure et al. 2016), 4-aminobenzoate (4-ABA) (Kubota et al. 2016), and 4-hydroxybenzoate (4-HBA) (Kitade et al. 2018) at a markedly high titer highlighted great potential of this microbe as a platform for commercial production of value-added aromatic and related chemicals from renewable sugar feedstocks. In this review, we summarize recent advances in metabolic engineering of *C. glutamicum* focusing on the production of these recently explored groups of value-added chemicals.

Suitability of *C. glutamicum* for production of aromatic compounds and derivatives

Whereas *C. glutamicum* is a well-known traditional aromatic amino acid producer and has been studied in this context for many years (Ikeda. 2006), this microbe's potential to produce other aromatic compounds had not been explored until recently. This could be partly attributed to the intrinsic ability of this microbe to degrade and assimilate various aromatic compounds such as benzoate, 4-HBA, phenol, PCA, cinnamic acid, caffeic acid, and ferulic acid (Brinkrolf et al. 2006; Shen and Liu 2005; Shen et al. 2012). However, the presence of such multiple pathways for aromatics metabolism would be an advantage to create aromatic-producing strain since interception of these pathways may lead to the accumulation of aromatic intermediates such as PCA. Moreover, it has become evident that *C. glutamicum* exhibits higher resistance to various toxic aromatic compounds such as phenol, protocatechuate, 4-HBA, and 4-ABA, compared to other industrial microbes such as *E. coli*, *Bacillus subtilis*, or *Pseudomonas putida* (Kitade et al. 2018; Kubota et al. 2016). Such high tolerance would be attributed to the

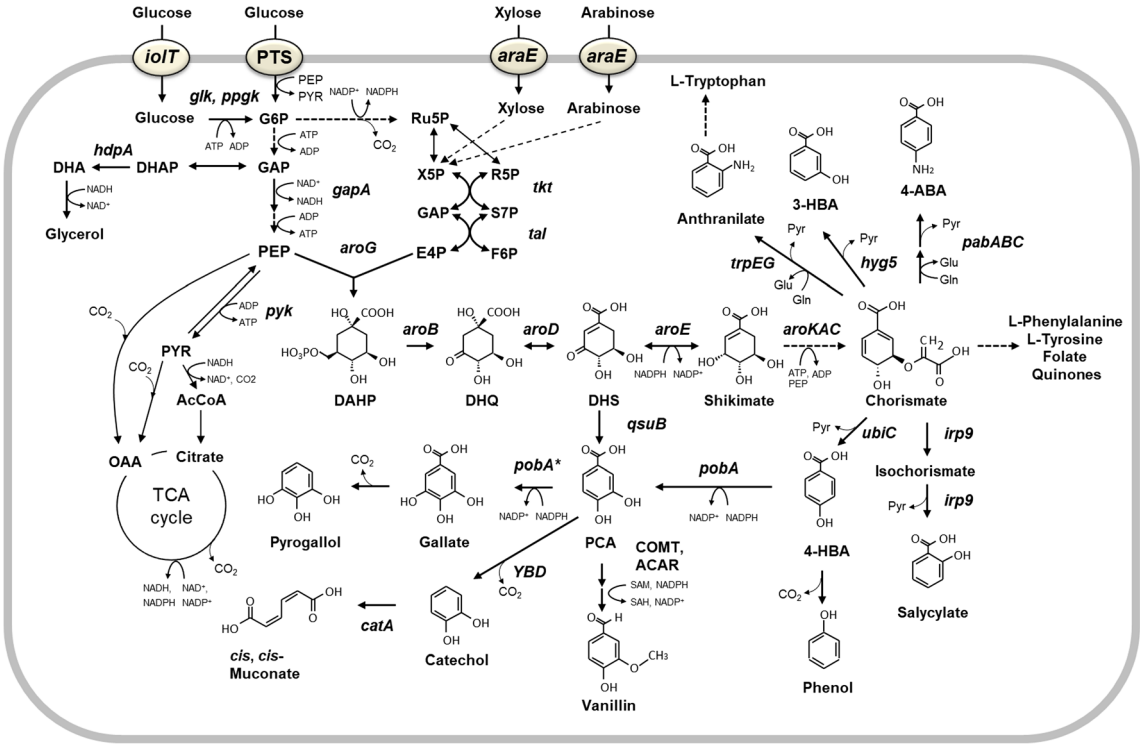

Fig. 1 Metabolic pathways for synthesis of shikimate pathway metabolites and derivative aromatic compounds in engineered *C. glutamicum*. Potential metabolic pathways that can be created by recruiting heterologous enzymes are also depicted. Genes encoding enzymes for corresponding catalytic steps are indicated in italics. G6P, glucose-6-phosphate; GAP, glyceraldehyde-3-phosphate; DHAP, 1,3-dihydroxyacetone phosphate; DHA, 1,3-dihydroxyacetone; PEP, phosphoenolpyruvate; PYR, pyruvate; AcCoA, acetyl-coenzyme A; OAA, oxaloacetate; Ru5P, ribulose-5-phosphate; R5P, ribose-5-phosphate; X5P, xylulose-5-phosphate; S7P, sedoheptulose-7-phosphate; E4P, erythrose 4-phosphate; DAHP, 3-deoxy-D-arabinoheptulosonate-7-phosphate; DHQ, 3-dehydroquinate; DHS, 3-dehydroshikimate; PCA, protocatechuate. Genes and coded enzymes: PTS, glucose-specific sugar:phosphoenolpyruvate phosphotransferase; *iolT*, *myo*-inositol permease; *araE*, pentose transporter; *glk*, glucokinase; *ppgk*, polyphosphate glucokinase; *tkt*, transketolase; *tal*, transaldolase; *gapA*, glyceraldehyde 3-phosphate dehydrogenase; *hdpA*, DHAP phosphatase; *aroG*, DAHP synthase; *aroB*, dehydroquinate synthase; *aroD*, dehydroquinate dehydratase; *aroE*, shikimate dehydrogenase; *aroKAC*, shikimate kinase, 5-enolpyruvyl shikimate-3-phosphate synthase, and chorismate synthase; *qsuB*, DHS dehydratase; *pobA*, 4-HBA 3-hydroxylase; *pobA**, mutated *pobA*; *catA*, catechol 1,2-dioxygenase; *ubiC*, chorismiate pyruvate lyase; *irp9*, isochorismate synthase/isochorismate pyruvate lyase (salitylate synthase); *hyg5*, chorismatase (3-HBA synthase); *trpEG*, anthranilate synthase; *pabABC*, 4-amino 4-deoxychorismate (ADC) synthase and ADC lyase, COMT, catechol-O-methyltransferase; ACAR, aromatic carboxylic acid reductase; YBD, PCA decarboxylase

characteristic outer membrane-like structure (mycomembrane) mainly composed of coryno-mycolic acids that would function as permeability barrier against toxic aromatic compounds (Laneelle et al. 2013). High tolerance to toxic aromatic products would be a crucial factor for their production at high titer, which is required for the commercialization of bioprocess, and it is considered to contribute to the high productivity of engineered *C. glutamicum* strains overproducing shikimate, 4-HBA, and 4-ABA (Fig. 1 and Table 1).

Production of shikimate as a value-added hydroaromatic compound

In microbes and plants, most aromatic compounds are synthesized via the shikimate pathway as a common pathway for aromatic compound biosynthesis. This pathway serves an essential role in those organisms as the source of aromatic amino acids and other physiologically important secondary metabolites like vitamins (e.g., folate and quinones), siderophores, or antibiotics (Fig. 1). Since the shikimate pathway represents a source for a wide range of commercially relevant compounds with very diverse biological activities and industrial applications, its engineering has gained increasing attention for efficient production of pathway intermediates like shikimate as well as various compounds derived from this pathway (Jiang and Zhang 2016; Lee and Wendisch 2017; Rodriguez et al. 2014). The first and committed step in the shikimate pathway is the condensation reaction of phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P) to generate 3-deoxy-D-arabinoheptulosonate-7-phosphate (DAHP), a reaction catalyzed by DAHP synthase. DAHP is then converted to chorismate, a branching point metabolite for aromatics synthesis, via six sequential reactions in this pathway.

Table 1 Summary of reports on the production of aromatics and related compounds by engineered *C. glutamicum* strains

Target compound	Host strain	Carbon source	Gene(s) (over)expressed or upregulated[a]	Gene(s) knocked out or downregulated	Titer (g/L)	Yield[b] (%)	Culti-vation time (h)	Culture style	Reference
Shikimate	*C. glutamicum* R	Glucose	OE: *aroB*, *aroD*, *aroE*, *iolT1*, *glk1*, *glk2*, *ppgk*, *tkt*, *tal*, *gapA* HE: $aroG^{S180F}$ (*E. coli*)	*ldhA*, *aroK*, *qusB*, *qsuD*, *ptsH*, *hdpA*	141	51	48	Fermenter	Kogure et al. (2016)
	C. glutamicum Res167	Sucrose	OE: *aroG*, *aroB*, *aroD*, *aroE* HE: *mgsA* (*E. coli*), DKFPS, ADTHS, DHQS (*Methanosarcina mazei*)	*aroK*	4.7	NA	NA	Flasks	Zhang et al. (2015a)
	C. glutamicum Res167	Sucrose	OE: *aroG*, *aroB*, *aroD*, *aroE*	*aroK*	11.3	24	NA	Fermenter	Zhang et al. (2015b)
	C. glutamicum Res167	Sucrose	OE: *aroG*, *aroB*, *aroD*, *aroE*, *tkt*	*aroK* downregulation: *pyk*, ncgl1856	23.8	NA	NA	Fermenter	Zhang et al. (2016)
PCA	*C. glutamicum* ATCC21420	Glucose	HE: *ubiC* (*E. coli*)		1.1	1.1	96	Fermenter	Okai et al. (2016)
	C. glutamicum ATCC21420	Ferulic acid	HE: *vanAB* (*Corynebacterium efficiens*)		1.1	43.2	12	Fermenter	Okai et al. (2017)
	C. glutamicum MB001	Glucose	OE: *qsuB* (*C. glutamicum*), *tkt*, P_{O6}-*iolT1* HE: *aroF** (*E. coli*)	cg0344-47, cg2625-40, cg1226, cg0502, cg3349-54, P_{dapA}-*gltA*	2.0	NA	48	Flasks	Kallscheuer and Marienhagen (2018)
Salicylate (2-HBA)	*C. glutamicum* MB001	Glucose	HE: *Irp9* (*Yercinia enterocolitica*), *aroF** (*E. coli*)	*cg0344-47, cg2625-40, cg1226, cg0502, cg3349-54,*	0.01	NA	48	Flasks	Kallscheuer and Marienhagen (2018)
3-HBA	*C. glutamicum* MB001	Glucose	OE: *tkt*, P_{O6}-*iolT1* HE: *hyg5* (*Streptomyces hygroscopicus*), *aroF** (*E. coli*)	cg0344-47, cg2625-40, cg1226, cg0502, cg3349-54, P_{dapA}-*gltA*	0.3	NA	48	Flasks	Kallscheuer and Marienhagen (2018)
4-HBA	*C. glutamicum* R	Glucose	OE: *tkt-tal*, *aroCKB*, *aroD*, *aroA*, *aroE* HE: $aroG^{S180F}$ (*E. coli*), *ubiC* (*Providencia rustigianii*)	*ldhA*, *qsuB*, *qsuD*, *pobA*, *poxF*, *pyk*, *hdpA*	36.6	41	24	Fermenter	Kitade et al. (2018)
	C. glutamicum MB001	Glucose	OE: *tkt*, P_{O6}-*iolT1* HE: *ubiC* (*E. coli*), *aroH* (*E. coli*)	cg0344-47, cg2625-40, cg1226, cg0502, cg3349-54, P_{dapA}-*gltA*	3.3	NA	48	Flasks	Kallscheuer and Marienhagen (2018)
3, 4-AHBA	*C. glutamicum* ATCC21799	Sweet sorghum juice	HE: *griH*, *griI* (*Streptomyces griseus*)		1.0	NA	72	Flasks	Kawaguchi et al. (2015)
4-ABA	*C. glutamicum* R	Glucose	OE: *aroCKB*, *aroD*, *aroA*, *aroE* HE: $aroG^{S180F}$, *pabAB* (*Corynebacterium callunae*), *pabC* (*Xenorhabdus bovienii*)	*ldhA*	43	20	48	Fermenter	Kubota et al. (2016)
cis, *cis*-Muconate	*C. glutamicum* ATCC13032	Glucose	OE: *qsuB* HE: *YBD*	*aroE*, *pcaGH*, *catB* *ptsI*, *iolR*	4.5	22	72	Tube	Shin et al. (2018)

[a] Types of expressed gene(s): HE, heterologous gene(s); OE, endogenous gene(s). The source organisms of heterologous genes are described in parentheses

[b] The yield is based on mol/mol of consumed sugar

NA, not available

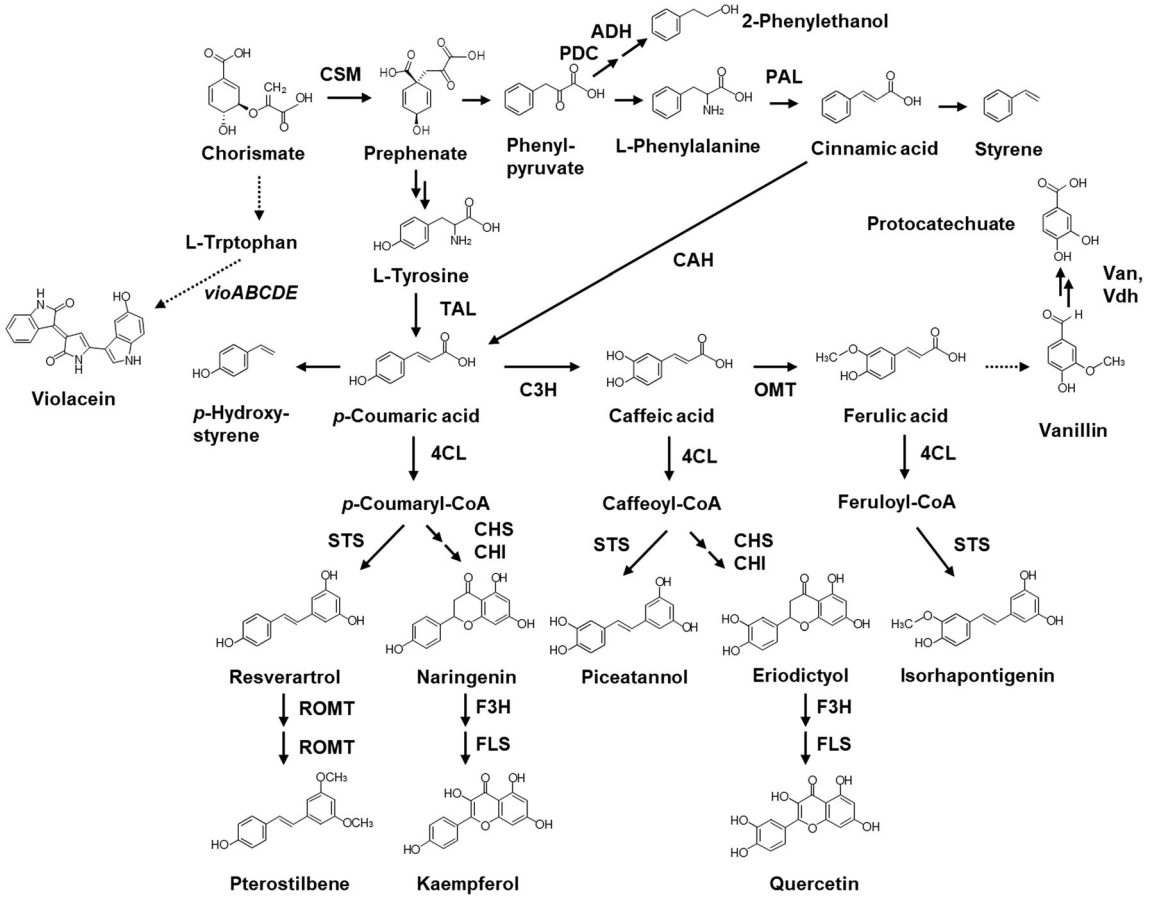

Fig. 2 Metabolic pathways for synthesis of plant polyphenols and other aromatic compounds derived from aromatic amino acids in engineered *C. glutamicum*. Potential metabolic pathways that can be created by recruiting heterologous enzymes are also depicted. CSM, chorismate mutase; PDC, phenylpyruvate decarboxylase; ADH, alcohol dehydrogenase; CAH, cinnamic acid 4-hydroxylase; PAL, phenylalanine ammonia lyase; TAL, tyrosine ammonia lyase; CAH, cinnamic acid hydroxylase; 4CL, 4-coumarate: CoA ligase; STS, stilbene synthase; CHS, chalcone synthase; CHI, chalcone isomerase; ROMT, resveratrol-di-*O*-methyltransferase; F3H, flavanone 3-hydroxylase; FLS, flavonol synthase; Van, vanillate-*O*-demethylase; Vdh, vanillin dehydrogenase

It is well-known that in both *C. glutamicum* and *E. coli*, carbon flow through the shikimate pathway is primarily controlled at the first reaction catalyzed by DAHP synthases, which are feedback inhibited by aromatic amino acids. For this reason, overexpression of feedback-resistant forms of DAHP synthases represents general approach to improve aromatic production derived from shikimate pathway. (Frost and Draths 1995; Ikeda 2006; Kramer et al. 2003).

Shikimate, a hydroaromatic compound formed as an intermediate of the shikimate pathway, is recently attracting attention as a building block chemical used crucially for the synthesis of an anti-influenza drug oseltamivir (Tamiflu®) (Martinez et al. 2015; Rawat et al. 2013; Tripathi et al. 2015). It also has a broad range of potential applications for pharmaceuticals and cosmetics such as a skin whitening agent and a hair-growing agent. Shikimate production currently depends on a low-yielding and costly extraction from the fruits of *Illicium* plants, which cannot meet the increasing demand for this compound (Bochkov et al. 2012; Ghosh et al. 2012; Rawat et al. 2013). This results in the large fluctuation of its market price from $40/kg to $1000/kg due to a huge demand of this compound for Tamiflu® synthesis along with outbreaks of human and avian influenza viruses (Rawat et al. 2013). In this context, microbial production of this compound from renewable sugars has been extensively studied as a promising alternative (Ghosh et al. 2012; Gu et al. 2017; Kramer et al. 2003; Martinez et al. 2015; Rawat et al. 2013; Rodriguez et al. 2013).

Microbial de novo production of shikimate from glucose was first achieved by engineering *E. coli* by the Frost group (Draths et al. 1999; Knop et al. 2001). In the engineered strain, *aroK* and *aroL* genes for shikimate kinase were disrupted to block shikimate pathway after shikimate synthesis and carbon flux to the same pathway was enhanced by introducing $aroF^{fbr}$ (feedback-resistant form of DAHP synthase), *aroB* (DHQ synthase), *aroE* (shikimate dehydrogenase), and *tkt* (transketolase). Further, availability of the precursor PEP was improved by employing non-PEP-consuming glucose uptake system consisting of the *glf*-encoded glucose facilitator and *glk*-encoded glucokinase from *Zymomonas mobilis* instead of endogenous phosphotransferase system (PTS) that

Table 2 Summary of reports on the production of plant polyphenols by engineered *C. glutamicum* strains

Target compound	Host strain	Carbon source	Gene(s) (over)expressed or upregulated[a]	Gene(s) knocked out or downregulated	Titer (mg/L)	Culture style	Reference
Violacein	*C. glutamicum* ATCC21850	Glucose	HE: *vioABCDE* (*Chromobacterium violaceum*)		5400	Fermenter	Sun et al. (2016)
Naringenin	*C. glutamicum* MB001	*p*-coumaric acid	HE: *4cl* (*Petroselinum crispum*), *chs*, *chi* (*Petunia* × *hybrida*)	cg0344-47, cg2625-40, cg1226	35	Flasks	Kallscheuer et al. (2016)
	C. glutamicum MB001	Glucose	HE: *aroH* (*E. coli*), *tal* (*Flavobacterium johnsoniae*), *sts* (*Arachis hypogaea*), *4cl* (*P. crispum*)	cg0344-47, cg2625-40, cg1226, cg0502	32	Flasks	Kallscheuer et al. (2016)
Eriodictyol	*C. glutamicum* MB001	Caffeic acid	HE: *4cl* (*P. crispum*), *chs*, *chi* (*P. hybrida*)	cg0344-47, cg2625-40, cg1226	37	Flasks	Kallscheuer et al. (2016)
Pinosylvin	*C. glutamicum* MB001	Cinnnamic acid	HE: *sts* (*A. hypogaea*), *4cl* (*P. crispum*)	cg0344-47, cg2625-40, cg1226	121	Flasks	Kallscheuer et al. (2016)
Resveratrol	*C. glutamicum* MB001	*p*-coumaric acid	HE: *sts* (*A. hypogaea*), *4cl* (*P. crispum*)	cg0344-47, cg2625-40, cg1226	158	Flasks	Kallscheuer et al. (2016)
	C. glutamicum MB001	4-HBA	HE: *sts* (*A. hypogaea*), *4cl* (*P. crispum*), *hbcL1*, ebA5319, ebA5320, ebA5318 (*Aromatoleum aromaticum*)	cg0344-47, cg2625-40, cg1226, cg0502	5	Flasks	Kallscheuer et al. (2017b)
	C. glutamicum MB001	Glucose	HE: *aroH* (*E. coli*), *tal* (*F. johnsoniae*), *sts* (*A. hypogaea*), *4cl* (*P. crispum*)	cg0344-47, cg2625-40, cg1226, cg0502	59	Flasks	Kallscheuer et al. (2016)
Piceatannol	*C. glutamicum* MB001	Caffeic acid	HE: *sts* (*A. hypogaea*), *4cl* (*P. crispum*)	cg0344-47, cg2625-40, cg1226	56	Flasks	Kallscheuer et al. (2016)
Pterostilbene	*C. glutamicum* MB001	*p*-coumaric acid	HE: *sts* (*A. hypogaea*), *4cl* (*P. crispum*), *malE* (*E. coli*)-*omt* (*Vitis vinifera*)	cg0344-47, cg2625-40, cg1226, cg0502	42	Flasks	Kallscheuer et al. (2017a)
Kaempferol	*C. glutamicum* MB001	*p*-coumaric acid	HE: *4cl* (*P. crispum*), *chs*, *chi* (*P. hybrida*), *f3h* (*P. hybrida*), *fls* (*Populas deltoides*)	cg0344-47, cg2625-40, cg1226, cg0502	23	Flasks	Kallscheuer et al. (2017a)
Quercetin	*C. glutamicum* MB001	Caffeic acid	HE: *4cl* (*P. crispum*), *chs*, *chi* (*P. hybrida*), *f3h* (*P. hybrida*), *fls* (*P. deltoides*)	cg0344-47, cg2625-40, cg1226, cg0502	10	Flasks	Kallscheuer et al. (2017a)

[a] Types of expressed gene(s): HE, heterologous gene(s); OE, endogenous gene(s). The source organisms of heterologous genes are described in parentheses

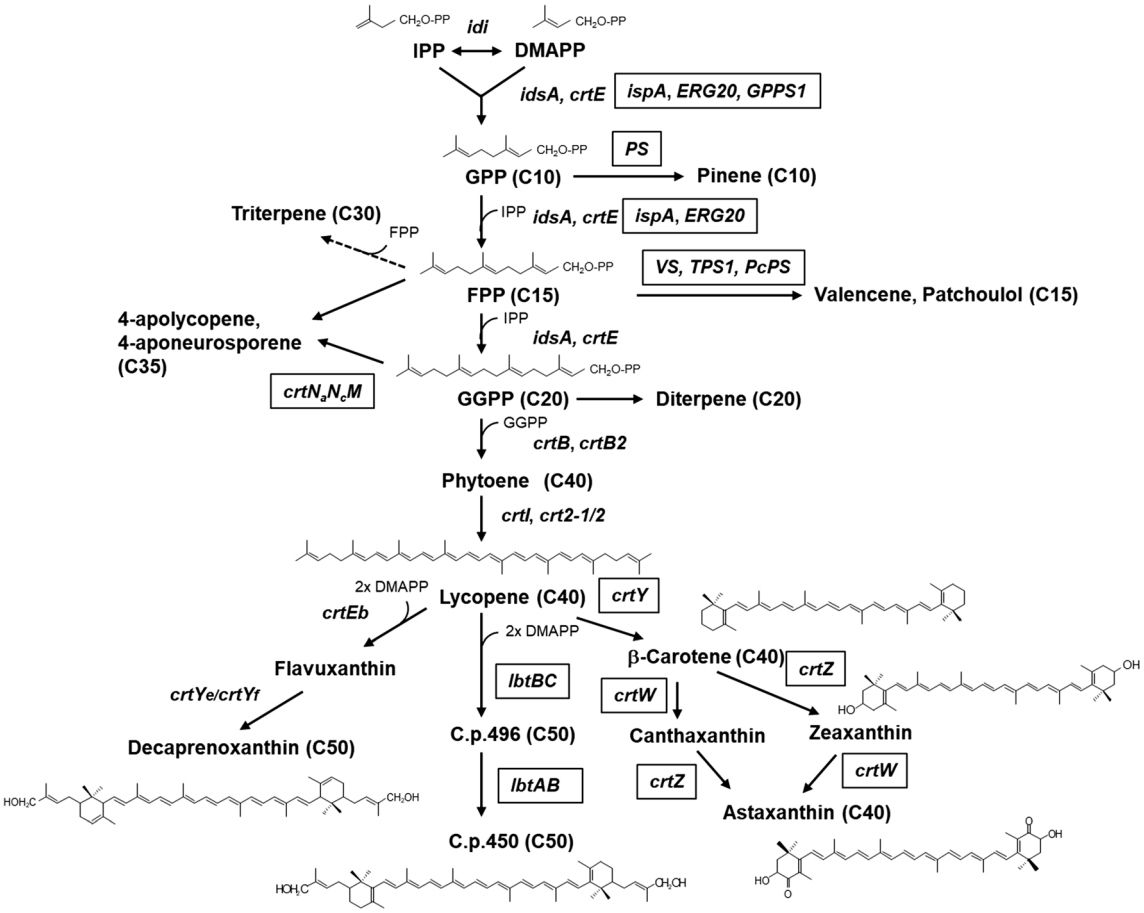

Fig. 3 Biosynthetic pathways for endogenous and heterologous carotenoids and other terpenoids in engineered *C. glutamicum*. Genes encoding enzymes for corresponding catalytic steps are indicated in italics. Heterologously expressed genes are illustrated in frames. IPP, isopentenyl pyrophosphate; DMAPP, dimethylallyl pyrophosphate; GPP, geranyl pyrophosphate; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; *idi*, isopentenyl-diphosphate isomerase; *idsA*, *crtE*, *ispA*, *ERG20*, and *GPPS1*, geranylgeranyl diphosphate synthase; *PS*, pinene synthase; VS and *TPS1*, (+)-valencene synthase; *PcPS*, plant patchoulol synthase; *crtB* and *crtB2*, phytoene synthase; *crtI* and *crt2-1/2*, phytoene desaturase; *crtEb*, lycopene elongase; *crtY*$_e$/*crtY*$_f$, carotenoid-ε-cyclase; *crtY*, lycopene β-cyclase; *crtZ*, β-carotene hydroxylase; *crtW*, β-carotene ketolase; *lbtBC*, lycopene elongase; *lbtAB*, carotenoid-ε-cyclase; *crtN*$_a$*N*$_c$*M*, dehydrosqualene synthase (*crtN*$_a$), aldehyde dehydrogenase (*crtN*$_c$), and aldehyde desaturase (*crtM*)

consumes PEP along with glucose uptake (Chandran et al. 2003). The resulting strain produced 87 g/L of shikimate at the yield of 36% (mol/mol) from glucose in fermentor. Following this study, other *E. coli* and *B. subtilis* strains have been engineered to produce shikimate by similar metabolic engineering approaches (Cui et al. 2014; Escalante et al. 2010; Johansson et al. 2005; Licona-Cassani et al. 2013; Liu et al. 2014a; Liu et al. 2014b; Rodriguez et al. 2013). However, the shikimate titer attained by these recombinants remained at low level that is not suitable for commercial application. On the other hand, we recently succeeded in the construction of shikimate-overproducing strain of *C. glutamicum* (Kogure et al. 2016). In the constructed strain, carbon flux from consumed sugar was redirected toward shikimate synthesis via overexpression of $aroG^{FBR}$ encoding a feedback-resistant form of DAHP synthase from *E. coli*, as well as endogenous genes for *aroB*, *aroD*, *aroE*, *tkt*, and *tal*, whereas consumption of shikimate and DHS was blocked by the deletion of *aroK*, *qsuB* (encoding DHS dehydratase), and *qsuD* (encoding quinate dehydrogenase) genes (Fig. 1). To improve PEP availability, PEP-consuming PTS was inactivated by disrupting the *ptsH* gene and an endogenous *myo*-inositol permease (*iolT1*) and glucokinases (*glk1* and *glk2* and *ppgk*) consisting PEP-independent glucose uptake route were overexpressed. Notably, glucose consumption of engineered strains was significantly increased by cumulative overexpression of *iolT1*, glucokinases, a rate-limiting glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, and the deletion of *hdpA* encoding 1,3-dihydroxyacetone phosphate phosphatase to inhibit loss to overflow byproducts 1,3-dihydroxyacetone (DHA) and glycerol. The enhanced glucose consumption concomitantly improved shikimate production. The resulting strain achieved production of 141 g/L shikimate from glucose with a yield of 51% (mol/mol) after 48 h in minimal medium in fermentor-controlled aerobic growth-arrested reaction (Table 1) (Kogure et al. 2016).

Table 3 Summary of reports on the production of carotenoids, other terpenoids, fatty acids, and other chemicals by engineered *C. glutamicum* strains

Target compound	Host strain	Carbon source	Gene(s) (over)expressed or upregulated[a]	Gene(s) knocked out or downregulated	Titer	Cultivation time (h)	Culture style	Reference
Lycopene	*C. glutamicum* ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI*	*crtEb*, *crtY*	0.79 mg/g CDW	24	Flasks	Heider et al. (2014a, b, c)
	C. glutamicum ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI*	*crtEb*	2.4 mg/g CDW	NA	Flasks	Heider et al. (2012)
Decapreno-xanchin	*C. glutamicum* MB001	Glucose	OE: *dxr*, *ispGH*, *ispDFE*, *dxs*, *idi*, *crtEbY*	*crtEb*, *crtY*	0.35 mg/g CDW	NA	Flasks	Heider et al. (2014a)
	C. glutamicum ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI*, *crtEbY*	*crtEb*, *crtY*	3.9 mg/g CDW	24	Flasks	Heider et al. (2014b)
C.p.450	*C. glutamicum* ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI* HE: *crtE2*, *crtY* (*Micrococcus luteus*)	*crtEb*, *crtY*	2.7 mg/g CDW	24	Flasks	Heider et al. (2014b)
Sarcinaxanthin	*C. glutamicum* ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI* HE: *lbtA*, *lbtBC* (*Dietzia* sp. CQ4)	*crtEb*, *crtY*	3.4 mg/g CDW	24	Flasks	Heider et al. (2014b)
ß-Carotene	*C. glutamicum* ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI* HE: $crtY_{Pa}$ (*Pantoea ananatis*)	*crtEb*, *crtY*	4.0 mg/g CDW	24	Flasks	Heider et al. (2014b)
	C. glutamicum MB001	Glucose	OE: *dxr*, *ispGH*, *ispDFE*, *dxs*, *crtEBI* HE: *crtYZ* (*P. ananatis*), *crtW* (*Brevundimonas aurantiaca*)	*crtEb*, *crtY*	2.1 mg/g CDW	NA	Flasks	Heider et al. (2014a)
	C. glutamicum MB001	Glucose	OE: *crtEBI*, *dxs*, *idi* HE: *crtY* (*P. ananatis*)	*crtEb*, *crtY*, cg0725	12 mg /g CDW	24	Flasks	Henke et al. (2016)
Zeaxanthin	*C. glutamicum* ATCC13032	Glucose	OE: *crtE*, *crtB*, *crtI* HE: $crtY_{Pa}$, $crtZ_{Pa}$ (*P. ananatis*)	*crtEb*, *crtY*	0.9 mg/g CDW	24	Flasks	Heider et al. (2014b)
	C. glutamicum MB001	Glucose	OE: *dxr*, *ispGH*, *ispDFE*, *dxs*, *crtEBI* HE: *crtYZ* (*P. ananatis*), *crtW* (*B. aurantiaca*)	*crtEb*, *crtY*	1.2 mg/g CDW	NA	Flasks	Heider et al. (2014a)
Astaxanthin	*C. glutamicum* MB001	Glucose	OE: *dxr*, *ispGH*, *ispDFE*, *dxs*, *idi* HE: *crtYZ* (*P. ananatis*), *crtW* (*B. aurantiaca*)	*crtEb*, *crtY*	0.14 mg/g CDW	NA	Flasks	Heider et al. (2014a)
	C. glutamicum MB001	Glucose	OE: *dxr*, *ispGH*, *ispDFE*, *dxs*, *crtEBI* HE: *crtYZ* (*P. ananatis*), *crtW* (*B. aurantiaca*)	*crtEb*, *crtY*	1.2 mg/g CDW	NA	Flasks	Heider et al. (2014a)
	C. glutamicum MB001	Glucose	OE: *crtEBI*, *dxs*, *idi* HE: *crtY* (*P. ananatis*), *crtW*, *crtZ* (*Fulvimarina pelagi*)	*crtEb*, *crtY*, cg0725	1.6 mg/g CDW	24	Flasks	Henke et al. (2016)
α-Pinene	*C. glutamicum* ATCC13032	Glucose	OE: *dxs*, *idi* HE: PS (*Pinus taeda*), GPPS (*Abies grandis*)		176 μg/L	48	Flasks	Kang et al. (2014)
(+)-Valencene	*C. glutamicum* ATCC13032	Glucose	HE: *ispA* (*E. coli*), CnVS (*Nootka cypress*)	*crtE*, *idsA*	2.4 mg/L (0.25 mg/CDW)	48	Flasks	Frohwitter et al. (2014)
(+)-Valencene	*C. glutamicum* ATCC13032	Glucose	HE: *ispA* (*E. coli*), CnVS (*Callitropsis nootkatensis*), *dxs*, *idi*	*crtE*, *idsA*	41 mg/L	24	Flasks	Binder et al. (2016)
Patchoulol	*C. glutamicum* ATCC13032	Glucose	OE: *dxs*, *idi* HE: *ispA* (*E. coli*), PS (*Pogostemon cablin*)	*crtOP*(cg0717-cg0723) *idsA*, *crtB2I'I2*	60 mg/L	142	Fermenter	Henke et al. (2018)
4-Apolycopene	*C. glutamicum* KCTC 1857	Glucose	HE: $crtN_aN_cM$ (*Planococcus* sp.)		NA	NA	Flasks	Ravikumar et al. (2018)
Fatty acids	*C. glutamicum* ATCC13032	Glucose	$fasA63^{up}$, *fasA2623*	*fasR20*	280 mg/L	24	Flasks	Takeno et al. (2013)
Fatty acids (including triacylglycerol)	*C. glutamicum* ATCC13032	Glucose	OE: *tesA*, *fadD*		3.0 g/L	48	Flasks	Plassmeier et al. (2016)

Table 3 (continued)

Target compound	Host strain	Carbon source	Gene(s) (over)expressed or upregulated[a]	Gene(s) knocked out or downregulated	Titer	Cultivation time (h)	Culture style	Reference
			HE: *aft1*, *aft2*, *tadA* (*R. opacus*), *pgpB* (*E. coli*)	*lip1*, *lip2*, cg2849, cg1320, cg1676, *fasR*, *ldh*, *pqo*				
Shinorine	*C. glutamicum* ATCC13032	Gluconic acid	OE: *gnd* HE: *amir4256-4259* (*Actynosynnema mirum*)	*ldhA*, *tal*	19.1 mg/L	72	Flasks	Tsuge et al. (2018)

[a] Types of expressed gene(s): HE, heterologous gene(s); OE, endogenous gene(s). The source organisms of heterologous genes are described in parentheses

NA, not available

Furthermore, similar productivity could be achieved by the simultaneous assimilation of glucose, xylose, and arabinose, allowing efficient shikimate production from lignocellulosic feedstocks (Table 1) (Kogure et al. 2016). The obtained titer and yield represented highest reported values not only for microbial production of shikimate but also for microbial aromatic production (Averesch and Kromer 2018). Considering the fact that the highest titer of aromatic compounds obtained by engineered yeast is only 3.1 g/L (Suastegui and Shao 2016), the above-mentioned results highlighted the superior potential of *C. glutamicum* to produce aromatic compounds derived from shikimate pathway.

Metabolically engineered *C. glutamicum* strains for shikimate production were also constructed recently by Zhang and colleagues. They utilized several genetic engineering techniques for strain construction such as CRISPRi system-mediated transcriptional regulation (Zhang et al. 2016), construction of genetic modules using ribosome binding site libraries (Zhang et al. 2015b), and introduction of a archaeal shikimate synthesis pathway (Zhang et al. 2015a). These approaches achieved shikimate production at 23.8, 11.3, and 4.7 g/L, respectively, in a fermenter or shake flask experiments (Table 1).

Production of protocatechuate and its derivatives

PCA (3, 4-dihydroxybenzoate) is a natural aromatic compound formed by several microbes and plants from a shikimate pathway intermediate 3-dehydroshikimate (DHS) and/or 4-HBA as direct precursors (Fig. 1). In the microbial aromatics metabolism, it represents a key precursor (a hub compound) for the biosynthesis of a wide range of value-added aromatic and related chemicals such as catechol, *cis*, *cis*-muconate (ccMA), adipate, gallate, pyrogallol, and vanillin (Fig. 1), as well as a common intermediate for degradation and assimilation of several aromatics (Shen et al. 2012). PCA itself is a valuable compound as a promising building block for synthesizing biopolymers. Moreover, it exhibits various pharmacological properties including antioxidant, anti-aging, anti-inflammatory, and anti-tumorigenic activities, and it has potential to be used in pharmaceuticals, functional foods, and cosmetic fields (Kakkar and Bais 2014; Krzysztoforska et al. 2017). While PCA is currently obtained by extraction from plant sources (Kakkar and Bais 2014; Krzysztoforska et al. 2017), more efficient fermentative production is desired. Microbial PCA production from glucose was first reported as an intermediate compound toward the production of catechol, which is a versatile organic building block for chemical industry (Li et al. 2005). In this study, PCA was produced via the shikimate pathway intermediate DHS by exploiting *aroZ*-encoded DHS dehydratase from *Klebsiella pneumoniae*

in a strain where *aroE*-encoded shikimate dehydrogenase is inactivated to interrupt the conversion of DHS along the shikimate pathway (Fig. 1). To increase the carbon flow to the shikimate pathway and to improve precursor availability, $aroF^{FBR}$-encoded feedback-resistant DAHP synthase, DHQ synthase (*aroB*), transketolase (*tktA*), and PEP synthase (*ppsA*) were overexpressed. The resultant engineered *E. coli* produced 41 g/L of PCA with a yield of 26% (mol/mol) from glucose, whereas PCA itself did not attract attention as a useful compound at that time (Li et al. 2005). On the other hand, Okai et al. recently reported PCA production in engineered *C. glutamicum* via an alternative production route. In this case, *E. coli ubiC*-encoded chorismate-pyruvate lyase (CPL) was overexpressed in a phenylalanine-producing *C. glutamicum* strain to convert chorismate into 4-HBA, which is further converted to PCA catalyzed by endogenous *pobA*-encoded 4-HBA hydroxylase. The resulting strain produced 1.1 g/L PCA from glucose after 96 h in the fermenter (Table 1) (Okai et al. 2016). They also developed an engineered *C. glutamicum* strain that could produce PCA from ferulic acid, an abundant lignin-derived phenolic compound in the plant biomass. They overexpressed vanillate *O*-demethylase genes *vanAB* from *Corynebacterium efficiens* in the PCA-producing host strain to convert ferulic acid into PCA via vanillate, which is formed via endogenous metabolic pathways. The resulting strain produced 1.1 g/L of PCA from 3.1 g/L of ferulic acid after 12 h in fed-batch fermenter biotransformation (Okai et al. 2017). Although the obtained PCA titer in these studies was far below the level applicable for practical use, the fact that engineered *C. glutamicum* can overproduce shikimate, and that PCA can be directly formed from the shikimate precursor DHS catalyzed by endogenous *qsuB*-encoded DHS dehydratase in the shikimate assimilation pathway strongly indicates that this bacterium has a potential to overproduce PCA as well.

Adipic acid and terephthalic acid are important platform chemicals as the building block of nylon-6,6 fiber and polyethylene terephthalate (PET), respectively (Sengupta et al. 2015). ccMA is a naturally occurring unsaturated dicarboxylic acid with extensive industrial applications as biological precursor for adipate and terephthalate (Polen et al. 2013; Xie et al. 2014). Bioproduction of ccMA from glucose via the shikimate pathway has also been pioneered in *E. coli* by the Frost group (Draths and Frost 1994; Niu et al. 2002). In this case, ccMA was synthesized by converting the shikimate pathway intermediate DHS via PCA and catechol by employing three heterologous enzymes: DHS dehydratase (AroZ) and PCA decarboxylase (AroY) from *K. pneumoniae* and a catechol 1,2-dioxygenase (CatA) from *Acinetobacter calcoaceticus*. As is the case of catechol production by engineered *E. coli*, shikimate dehydrogenase was inactivated to block the pathway below DHS and $aroF^{FBR}$-encoded feedback-resistant DAHP synthase, DHQ synthase (*aroB*), and transketolase (*tktA*) were overexpressed. The resulting strain produced 36.8 g/L of ccMA with 22% (mol/mol) yield from glucose in fed-batch fermentations (Niu et al. 2002). Following this study, de novo ccMA production via different pathways starting from chorismate and proceeds via either anthranilate, salicylate, 2,3-dihydroxybenzoate, or 4-HBA has been engineered in *E. coli*, *S. cerevisiae*, *P. putida*, and *K. pneumoniae* (Jung et al. 2015; Lin et al. 2014; Sengupta et al. 2015; Sun et al. 2013; Sun et al. 2014; Weber et al. 2012; Xie et al. 2014). With *C. glutamicum* as a host, Shin et al. recently engineered a strain producing ccMA from glucose (Shin et al. 2018). They introduced heterologous PCA decarboxylase gene into the host *C. glutamicum* strain where catabolic pathways for DHS, PCA, and ccMA were inactivated by deletion of the *aroE*, *pcaGH*, and *catB* genes encoding shikimate dehydrogenase, PCA 3,4-dioxygenase, and chloromuconate cycloisomerase, respectively. Moreover, to improve PEP availability for the shikimate pathway, a non-PTS strain that does not consume PEP along with glucose uptake was generated by the deletion of *ptsI* and *iolR* (a transcriptional repressor of *myo*-inositol utilization genes including *iolT1*) to inactivate PTS and to induce expression of a non-PTS glucose permease IolT1, respectively (Ikeda et al. 2011). The overexpression of *qsuB*-encoded DHS dehydratase further improved ccMA production to 4.5 g/L at a yield of 22% (mol/mol) after 48 h by fed-batch fermentation (Table 1). Thus, whereas the titer was low, the yield was comparable to the highest reported one that had been achieved with an engineered *E. coli* ccMA producer (36.8 g/L at 22% yield (mol/mol)) (Niu et al. 2002).

Other industrially important aromatic compounds that are derived from PCA include gallate (Chandran and Frost 2001; Chen et al. 2017; Kambourakis et al. 2000), pyrogallol (Chamkha et al. 2002; Kambourakis et al. 2000; Meier et al. 2017), and vanillin (Brochado et al. 2010; Brochado and Patil 2013; Hansen et al. 2009) (Fig. 1). Their microbial production from glucose and other sugars has been widely studied especially in *E. coli* and *S. cerevisiae* (Averesch and Kromer 2018; Lee and Wendisch 2017). While production of these compounds has not yet been reported in *C. glutamicum*, it would be possible by extending the endogenous metabolic pathway from PCA with responsible heterologous enzymes (Fig. 1).

Production of chorismate-derived phenolic acids and related compounds

Most aromatic compounds including aromatic amino acids are synthesized from chorismate, a metabolite located at metabolic branch point from the shikimate pathway. Several industrially important aromatics can be biosynthesized from chorismate via a limited number of reaction steps, which include 4-HBA, 4-ABA, 2-hydroxybenzoate (salicylate), 3-

hydroxybenzote, and anthranilate (Fig. 1). These phenolic acid aromatics represent typical bulk chemicals currently produced by chemical conversions from petroleum feedstocks. Therefore, their eco-friendly and sustainable bioproduction from renewable resources is needed. Microbial production of these phenolic acids has been widely researched by engineering model organisms such as *E. coli*, *S. cerevisiae*, and the solvent-tolerant bacterium *P. putida* (Gottardi et al. 2017; Lee and Wendisch 2017; Noda and Kondo 2017; Noda et al. 2016). However, to date, bioproduction of these phenolic acids has not been applied on a commercial basis because of low titers and yields. In contrast, recent studies revealed that *C. glutamicum* represents a promising microbial platform for their production at industrially applicable high productivity (Kitade et al. 2018; Kubota et al. 2016).

4-HBA is synthesized as a part of the ubiquinone biosynthesis pathway in several microbes and is a useful building block to produce liquid crystal polymers and paraben. While 4-HBA production systems have been developed in *K. pneumoniae*, *E. coli*, and *P. putida* (Barker and Frost 2001; Meijnen et al. 2011; Muller et al. 1995; Verhoef et al. 2007), their productivities were limited. Recently, Kitade et al. reported on 4-HBA overproduction by metabolically engineered *C. glutamicum*, which exhibited higher tolerance to 4-HBA toxicity than those previously reported microbes used for 4-HBA production (Kitade et al. 2018). In this study, all seven shikimate pathway genes and non-oxidative pentose phosphate pathway genes *tkt* and *tal* were overexpressed by their chromosomal integration to enhance the carbon flow into and through the shikimate pathway. To create the last step of 4-HBA biosynthesis from chorismate, which is not present in *C. glutamicum*, chorismate pyruvate-lyase (UbiC) encoded by *Providencia rustigianii ubiC*, which is shown to be highly resistant to feedback inhibition by 4-HBA, was overexpressed. Additionally, formation of major byproducts DHA and pyruvate was minimized by deletion of the *hdpA* and *pyk* genes encoding dihydroxyacetone phosphate phosphatase and pyruvate kinase, respectively. The resulting strain produced 36.6 g/L of 4-HBA from glucose with a yield of 41% (mol/mol) after 24 h in an aerobic growth-arrested bioprocess conducted in a fermenter with minimal medium (Table 1) (Kitade et al. 2018). This productivity represented the highest titer and yield of microbial 4-HBA production ever reported (Kitade et al. 2018), beyond those obtained in previous studies with *E. coli* (12 g/L at a yield of 13% (mol/mol)) (Barker and Frost 2001) or *S. cerevisiae* (90 mg/L at a yield of 0.8% (mol/mol))(Kromer et al. 2013).

Phenol is an important commodity chemical used as a raw material to produce phenolic plastics and pharmaceuticals and is currently produced from fossil resources. Microbial phenol production from glucose has been reported in *E. coli*, employing either tyrosine (Kim et al. 2014), 4-HBA (Thompson et al. 2016), or salicylate (Thompson et al. 2016) as a precursor that is converted to phenol via tyrosine phenol lyase, 4-HBA decarboxylase, or salicylate decarboxylase, respectively. However, microbial phenol production from renewable sugars has been limited due to its severe toxicity to host microorganisms and the maximal reported titer of phenol production is only 3.8 g/L (Kim et al. 2014). Since *C. glutamicum* exhibits high tolerance to many toxic aromatics (Kitade et al. 2018; Kubota et al. 2016) and engineered strain can overproduce 4-HBA, decarboxylation of 4-HBA by employing heterologous 4-HBA decarboxylase would be a favorable approach for bioproduction of phenol from sugars in this microbe.

4-ABA is a precursor compound for microbial folate biosynthesis in the pathway branched from chorismate. Biotechnologically, it has a great potential to serve as a building block of biopolymers including engineering plastics. Currently, 4-ABA is produced by chemical conversions from petroleum-derived toluene and its bioproduction from biomass resources is desired to address environmental issues. It is synthesized from chorismate via 4-amino-4-deoxychorismate (ADC) by consecutive reactions catalyzed by ADC synthase and ADC lyase encoded by the *pabABC* genes (Fig. 1). Kubota et al. recently reported on the metabolic engineering of *C. glutamicum* for 4-ABA overproduction. They screened heterologous *pabABC* genes that caused high 4-ABA production and found that overexpression of the *pabAB* from *Corynebacterium callunae* and the *pabC* from *Xenorhabdus bovienii* resulted in the highest 4-ABA production. Overexpression of these genes in a host strain overexpressing shikimate pathway genes resulted in production of 43 g/L of 4-ABA from glucose with a 20% yield (mol/mol) in fermentor, which represented the highest titer of 4-ABA produced by engineered microbes ever reported (Table 1) (Kubota et al. 2016). Intriguingly, it was shown that substantial part of the amino group of the product 4-ABA was unexpectedly converted to a *N*-glucosylated byproduct due to a non-enzymatical reaction between glucose used as a carbon source and the product 4-ABA during fermentation. Fortunately, this *N*-glucosylated byproduct could be easily reconverted to 4-ABA by acid treatment, preventing the loss of the product yield (Kubota et al. 2016).

In a recent study, Kallscheuer et al. engineered a *C. glutamicum* platform strain for the production of four industrially relevant hydroxybenzoates, i.e., PCA, salicylate, 3-hydroxybenzoate (3-HBA), and 4-HBA (Kallscheuer and Marienhagen 2018). Since *C. glutamicum* has a complex catabolic network for aromatic degradation and utilization that hamper aromatic production in this microbe, they constructed a platform *C. glutamicum* strain for aromatic production where 27 genes in five gene clusters comprising peripheral and central catabolic pathways of aromatics known in this microbe were deleted. This strain was subsequently engineered for the production of PCA, salicylate, 3-HBA, and 4-HBA by

overexpression of heterologous genes coding for QsuB (DHS dehydratase), Irp9 (isochorismate synthase/isochorismate pyruvate lyase or salicylate synthase), Hyg5 (3-HBA synthase), and UbiC (chorismate-pyruvate lyase), respectively (Fig. 1). Production of these compounds was optimized by engineering the key enzymatic activities of the central carbon metabolism toward increased precursor availability. These included overexpression of feedback-resistant DAHP synthases (AroH or AroF from *E. coli*), PEP-independent glucose permease IolT1, and transketolase as well as reduction of the *gltA*-encoded citrate synthase activity by promoter replacement to lower the carbon flux into the tricarboxylic acid (TCA) cycle. By combining these modifications, constructed strains produced 2.0 g/L PCA, 0.01 g/L salicylate, 0.3 g/L 3-HBA, and 3.3 g/L 4-HBA in shaking flasks (Table 1) (Kallscheuer and Marienhagen 2018).

3-Amino-4-hydroxybenzoate (3,4-AHBA) is a natural aromatic compound that is synthesized as a metabolic intermediate of grixazone biosynthesis in *Streptomyces griseus* (Suzuki et al. 2006). It is a valuable compound serving as a precursor for the synthesis of polybenzoxazole, a thermostable bioplastic. The products of the *griH* and *griI* genes of *S. griseus* are involved in the biosynthesis of 3,4-AHBA, where GriI catalyzes an aldol condensation reaction between L-aspartate-4-semialdehyde and dihydroxyacetonephosphate, whereas GriH converts the resulting C7 metabolite into 3,4-AHBA. Thus, this pathway represents a simple and novel route for aromatic (benzene ring) formation from C4 and C3 metabolites that is independent of the shikimate pathway or chorismate, which is responsible for the synthesis of most aromatic compounds (Suzuki et al. 2006). Exploiting this unique enzyme system, Kawaguchi et al. constructed an engineered *C. glutamicum* producing 3,4-AHBA by expressing the *griH* and *griI* genes from *S. griseus* in lysine-producing strain *C. glutamicum* ATCC21799. The constructed strain produced 1.0 g/L of 3,4-AHBA from sweet sorghum juice, which was used as alternative renewable feedstock to sugar cane molasses (Table 1) (Kawaguchi et al. 2015).

Production of plant polyphenols

Plant polyphenols constitute a large group of aromatic compounds of the secondary plant metabolism (Scalbert et al. 2005a). They exhibit diverse human and animal health-promoting activities such as antioxidant, anti-inflammatory, anti-microbial, anti-cancer, or anti-diabetic activities and thus have potential applications as food supplements, pharmaceuticals, and cosmetic ingredients. These compounds are synthesized from phenylpropanoids and thus can be produced by extending microbial endogenous aromatic amino acids (L-phenylalanine or L-tyrosine) production pathways by integrating heterologous plant biosynthetic pathways (Fig. 2). This fact promoted extensive researches on biotechnological production of various plant polyphenols such as flavonoids, stilbenoids, and coumarins in the past decade, mainly focusing on engineering *E. coli* and *S. cerevisiae* as production hosts (Horinouchi. 2008; Katsuyama et al. 2007; Liu et al. 2013a; Marienhagen and Bott 2013; Suastegui and Shao 2016; van Summeren-Wesenhagen and Marienhagen 2013; Wang et al. 2017; Gottardi et al. 2017; Mei et al. 2015). More recently, Kallscheuer and colleagues proved that engineered *C. glutamicum* is also suitable as a platform to produce plant polyphenols such as stilbenes and (2S)-flavanones (Kallscheuer et al. 2016). In case of *C. glutamicum*, which can degrade and assimilate various aromatic compounds (Shen et al. 2012), it was initially found that it can grow on phenylpropanoids as a sole carbon and energy source following unknown catabolic pathway (Kallscheuer et al. 2016). Accordingly, to achieve plant polyphenol production in this bacterium, they constructed a host *C. glutamicum* strain in which 21 genes involved in the catabolism of aromatic compounds were deleted to block catabolic degradation of aromatics including phenylpropanoids in this microbe (Shen et al. 2012). Particularly, deletion of the *phdBCDE* genes responsible for CoA-dependent β-oxidative chain-shortening pathway for phenylpropanoid degradation turned out to be the key step toward enabling polyphenol production in *C. glutamicum* (Kallscheuer et al. 2016). Subsequent overexpression of plant-derived genes encoding a chalcone synthase (CHS) and a chalcone isomerase (CHI) enabled formation of (2S)-flavanones: 35 mg/L naringenin and 37 mg/L eriodictyol, from corresponding phenylpropanoids *p*-coumaric acid and caffeic acid, respectively (Fig. 2) (Table 2). On the other hand, overexpression of genes encoding a 4-coumarate:CoA-ligase (4CL) and a stilbene synthase (STS) led to the production of the stilbenes: 121 mg/L pinosylvin, 158 mg/L resveratrol, and 56 mg/L piceatannol from corresponding phenylpropanoids cinnamate, *p*-coumarate, and caffeic acid, respectively (Fig. 2) (Table 2). Direct production of 59 mg/L resveratrol and 32 mg/L naringenin from glucose was also achieved through engineering of the upstream pathways by overexpression of *aroH* gene encoding feedback-resistant DAHP synthase from *E. coli* and a gene encoding tyrosine ammonia lyase from *Flavobacterium johnsoniae* as well as deletion of *qsuB* gene encoding DHS dehydratase (Table 2) (Kallscheuer et al. 2016).

Following this study, Kallscheuer N. et al. further extended the heterologous metabolic pathway originating from polyphenol core structures like stilbene resveratrol, (2S)-flavanone naringenin, and eriodictyol toward production of modified products of these compounds with an even higher commercial value (Kallscheuer et al. 2017a). Expression of an *O*-methyltransferase in a resveratrol-producing strain allowed synthesis of 42 mg/L of the di-*O*-methylated pterostilbene from *p*-coumaric acid (Fig. 2) (Table 2). Notably, increasing the

solubility of the *O*-methyltransferase by expressing it as a fusion protein with the maltose-binding protein of *E. coli* was required to obtain this titer. Similarly, expression of dioxygenase genes in (2S)-flavanone-producing strains enabled the production of the following flavonols: 23 mg/L of kaempferol and 10 mg/L of quercetin from *p*-coumaric acid and caffeic acid, respectively (Fig. 2) (Table 2) (Kallscheuer et al. 2017a). These results demonstrated that *C. glutamicum* is a favorable host organism for the production of complex plant polyphenols.

In a parallel study, Kallscheuer N. et al. constructed a novel biosynthetic pathway for resveratrol production from 4-HBA as a precursor based on the reverse reaction of a CoA-dependent, β-oxidative phenylpropanoid degradation pathway identified in the facultative denitrifying betaproteobacterium *Azoarcus* sp. EbN1 (Kallscheuer et al. 2017b). Engineered synthetic pathway produced *p*-coumaroyl-CoA from 4-HBA and acetyl-CoA by implemented β-oxidation pathway enzymes that is running in the non-natural direction, consisting of 4-HBA:CoA ligase, β-ketothiolase, 3-hydroxyacyl-CoA dehydrogenase, and enoyl-CoA hydratase from *Azoarcus* sp. EbN1. The overexpression of these genes alongside the heterologous stilbene synthase resulted in production of 5 mg/L of resveratrol from 4-HBA in engineered *C. glutamicum*. Thus, phenylpropanoid synthesis could be achieved without employing aromatic amino acids and a heterologous ammonia lyase, which represents a primary limiting step for microbial polyphenol synthesis (Table 2) (Kallscheuer et al. 2017b).

The biosynthetic pathway for aromatic amino acid has also been extended toward production of violacein, a tryptophan-derived bacterial purplish blue-colored indolocarbazole pigment with potential applications as a pharmaceutical due to its antibacterial, antitumoral, antiviral, and antioxidant activities (Choi et al. 2015b). Sun H. et al. recently engineered violacein-producing *C. glutamicum* strain by employing tryptophan-overproducing strain as a host and overexpressing violacein biosynthesis pathway genes *vioABCDE* from native violacein-producing bacterium *Chromobacterium violaceum*, which is involved in the condensation reaction of two tryptophan molecules to form violacein (Fig. 2). They overexpressed *vioABCDE* as a synthetic operon with an IPTG-inducible promoter and strong *C. glutamicum* ribosome-binding site (RBS) (Sun et al. 2016). The resulting strain produced 5.4 g/L of violacein in fed-batch fermentation in a bioreactor (Table 2), representing the highest titer and productivity to date. In contrast, the yield at 2.8% (mol/mol glucose) was lower than 6.0% (mol/mol glucose) previously achieved by engineered *E. coli* (Fang et al. 2015; Sun et al. 2016).

Derivatives of L-phenylalanine and L-tyrosine include other industrially important molecules, which include cinnamic acid, *p*-hydroxycinnamic acid, their decarboxylated metabolites styrene and *p*-hydroxystyrene, as well as caffeic acid, ferulic acid, and vanillin (Fig. 2). Metabolically engineered strains to produce these aromatic compounds have been constructed in *E. coli*, *S. cerevisiae*, and several other microbes by employing heterologous genes coding for appropriate enzymes, even though the productivity of most of these compounds remained at low level not applicable to practical use (Koma et al. 2012; Lee and Wendisch 2017; Noda and Kondo 2017; Vargas-Tah et al. 2015; Wang et al. 2017). While production of these compounds has not yet been reported in *C. glutamicum*, it would be possible by similarly extending aromatic amino acids biosynthetic pathways with corresponding heterologous catalytic steps (Fig. 2).

Production of carotenoids and other terpenoids

Carotenoids are important natural yellow- to red-colored pigments found ubiquitously in plants, fungi, algae, and bacteria, where they can have diverse functions such as photoprotection or light-harvesting molecules, membrane stabilizers, and precursors of hormones (Lee and Schmidt-Dannert 2002; Vershinin 1999). Carotenoids and other terpenoids are traditionally used in food, feed, and nutraceutical industries (Lee and Schmidt-Dannert 2002). To date, their diverse health-promoting activities due to their antioxidative properties have received more and more attention of the health care industry for possible applications as pharmaceuticals and nutraceuticals. All carotenoids are originating from the isoprenoid biosynthetic pathway and are derived from the universal isoprene units isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMPP) (Fig. 3) (Rodriguez-Villalon et al. 2008; Tippmann et al. 2013). These isoprenoid precursors are derived from the methylerythritol phosphate (MEP) pathway in *C. glutamicum* like in most bacteria (Rodriguez-Concepcion and Boronat 2002). Whereas carotenoids are currently produced by chemical synthesis or by isolation from natural sources, such production methods harbor problems of low yield, high cost, and/or difficulty of synthesis or extraction (Misawa 2011). In this context, their efficient microbial production offers a promising alternative.

Carotenoids are classified according to the lengths of their carbon backbone with the majority consisting of C40 backbone, and only a rare number of C30 and C50 carotenoids have been described. *C. glutamicum* belongs to a rare group of carotenogenic bacteria that naturally produces a rare cyclic C50 carotenoid decaprenoxanthin and its glycosides (Krubasik et al. 2001b), which are responsible for its characteristic yellow pigmentation. Recently, respective genes comprising the entire carotenogenic pathway in this microbe have been elucidated (Fig. 3) (Heider et al. 2014a; Krubasik et al. 2001a; Krubasik et al. 2001b). Based on this knowledge, potential of this organism to produce native and non-native carotenoids has been explored through genetic engineering of

the carotenoid biosynthesis pathway. Heider et al. engineered lycopene-producing *C. glutamicum* by deleting the *crtEb* gene-encoding lycopene elongase to prevent conversion of lycopene to decaprenoxanthin and by overexpression of *crtE*, *crtB*, and *crtI* genes encoding prenyl transferase, phytoene synthase, and phytoene desaturase, respectively, for conversion of geranylgeranyl pyrophosphate (GGPP) to lycopene (Fig. 3). The resulting strain showed intensely red-pigmented cells and produced 2.4 mg/g cell dry weight (CDW) lycopene (Table 3) (Heider et al. 2012). Based on the constructed lycopene-producing platform strain, *C. glutamicum* strains producing native and non-native C50 carotenoids decaprenoxanthin, C.p.450, and sarcinaxanthin, as well as non-native C40 carotenoids β-carotene and zeaxanthin, in the milligrams per CDW range have been engineered by overexpressing endogenous and/or heterologous carotenogenic genes (Fig. 3, Table 3) (Heider et al. 2014b). On the other hand, an endogenous gene, cg0730/*crtX*, responsible for glycosylation of carotenoids was identified, which enabled controlled glycosylation of formed carotenoids (Heider et al. 2014b).

C. glutamicum has also been engineered to produce several short-chain terpenoids with applications in perfume industry, including monoterpene pinene (Kang et al. 2014) and sesquiterpenes (+)-valencene (Binder et al. 2016; Frohwitter et al. 2014) and patchoulol (Fig. 3) (Henke et al. 2018). Pinene is a monoterpene (C10) naturally found in pine oil and has industrial applications in fragrances, flavors, and pharmaceuticals. Kang et al. constructed metabolically engineered *C. glutamicum* to produce pinene. They expressed geranyl diphosphate synthases (GPPS) and pinene synthases (PS) obtained from plants (*Pinus taeda* and *Abies grandis*) in a host strain overexpressing endogenous 1-deoxy-D-xylose-5-phosphate synthase (Dxs) and isopentenyl diphosphate isomerase (Idi), resulting in production of 27 μg/g CDW α-pinene (Fig. 3, Table 3) (Kang et al. 2014). Production of sesquiterpene, (+)-valencene, an aroma compound of citrus fruits used as flavor, was also achieved by engineering *C. glutamicum* (Binder et al. 2016; Frohwitter et al. 2014). Deletion of two endogenous prenyltransferase genes *crtE* and *idsA*, as well as overexpression of the heterologous farnesyl pyrophosphate (FPP) synthase gene *ispA* from *E. coli* and the (+)-valencene synthase gene from *Nootka cypress* allowed production of 2.4 mg/L (+)-valencene (Fig. 3, Table 3) (Frohwitter et al. 2014). More recently, sesquarterpenes as novel C35 carotenoids with antioxidant activity were synthesized by engineering *C. glutamicum* to express the *crtNaNcM* genes derived from the *Planococcus* sp. bacteria (Fig. 3) (Ravikumar et al. 2018). Various sesquarterpenes like 4-apolycopene (red-color) and 4-aponeurosporene (yellow-color) could be accumulated depending on the expression of the genetic elements of the *crtNaNcM* genes (Table 3) (Ravikumar et al. 2018).

Precursor availability is a key determinant to improve product yields, and in this regard, carotenogenesis was also engineered. Improved supply of the precursor IPP by overexpressing all of eight MEP pathway genes enhanced the production of lycopene, decaprenoxanthin, and astaxanthin by engineered *C. glutamicum* (Heider et al. 2014c). Improvement of the carotenogenesis is also examined via engineering of the regulation of gene expression. Henke et al. demonstrated that the MarR-type transcriptional regulator CrtR repressed carotenogenic genes in an isoprenoid pyrophosphate-dependent manner in *C. glutamicum* (Henke et al. 2017). They showed that deletion of the *crtR* gene represents a general strategy to increase production of native and non-native carotenoids. In addition to altering the regulation of a specific biosynthetic pathway, engineering of the global regulator has been shown to have a considerable impact on cellular metabolism (Taniguchi et al. 2017a; Taniguchi and Wendisch 2015). In this context, Taniguchi et al. demonstrated that overexpression of the primary sigma factor gene *sigA* increased production of native carotenoids lycopene and decaprenoxanthin as well as non-native carotenoids β-carotene and bisanhydrobacterioruberin (Taniguchi et al. 2017b). They also showed that deletion of the gene for the alternative sigma factor SigB also increased carotenoid production. On the other hand, Binder et al. recently developed a gene expression control system employing light-responsive photocaged IPTG to precisely control the timing of gene expression that triggers toxic product formation. This regulatory system was successfully employed to improve the production of (+)-valencene, which is a toxic compound inhibiting cell growth, via the control of the time point of light induction for its biosynthesis genes (Binder et al. 2016).

Production of fatty acids and lipids

Microbial production of fatty acids, lipids, and related compounds has attracted attention as a renewable source of biofuels as well as functional nutrients. Studies on microbial lipid production have been advanced in naturally oleaginous fungi (Sakuradani et al. 2013), yeasts (Beopoulos et al. 2011), and algae (Han et al. 2015), while naturally non-oleaginous bacteria like *E. coli* (Dellomonaco et al. 2011; Lennen and Pfleger 2012; Steen et al. 2010) and *C. glutamicum* have also been researched more recently for the potential of fatty acid and lipid production. Regarding fatty acid and lipid metabolism, *C. glutamicum* has several inherent properties that is distinct from that in most bacteria such as *E. coli* and *B. subtilis*, which include the presence of eukaryotic multifunctional type I fatty acid synthase (FAS-I) system comprising FAS IA and FAS IB, the absence of the fatty acids β-oxidation pathway involved in their degradation, as well as the presence of high cytoplasmic thioesterase (TES) activity that is involved in the formation of free fatty acids from acyl (ACP)-CoA (Takeno et al. 2013). Takeno and colleagues

isolated an oleic acid-secreting mutant of *C. glutamicum* by isolating spontaneous mutants resistant to palmitic acid ester surfactant tween 40 and cerulenin, an inhibitor of fatty acid biosynthesis. The whole genome analysis of the resultant mutant specified responsible mutations for oleic acid-secreting phenotype in *fasR* encoding fatty acid biosynthesis repressor (Nickel et al. 2010) and in *fasA* encoding FAS IA. Reconstitution experiments in the wild-type strain demonstrated that only the *fasR* mutation could trigger oleic acid secretion. In this reconstituted *fasR* mutant, fatty acid biosynthetic pathway genes *fasA*, *fasB* (encoding FAS IB), and *accD1* (encoding the β-subunit of acetyl-CoA carboxylase) were shown to be upregulated, indicating that *fasR* mutation caused functional impairment of its product (FasR repressor). These results revealed that derepression of fatty acid biosynthesis leads to an oversupply of acyl-CoAs, which would be converted into free fatty acids catalyzed by high endogenous acyl-CoA thioesterase activity and excreted without degradation due to the absence of fatty acid β-oxidation pathway in *C. glutamicum* (Takeno et al. 2013). The reconstructed strain harboring three causative mutations in the wild-type background produced 280 mg/L of fatty acids, which consisted mainly of oleic acid (208 mg/L) and palmitic acid (47 mg/L) showing the potential of *C. glutamicum* to produce fatty acids and related functional lipids (Table 1) (Takeno et al. 2013). Apart from fatty acid biosynthesis, *fasA*- and *fasB*-encoded FAS-I system was shown to have important physiological roles in the biosynthesis of cofactors biotin and alpha-lipoic acid in an engineered biotin-prototrophic *C. glutamicum* strain as the source of the precursors of these cofactors in this organism (Ikeda et al. 2017).

On the other hand, Plassmeier et al. engineered *C. glutamicum* to produce triacylglycerol (TAG) (Plassmeier et al. 2016). They completed a functional TAG biosynthesis pathway in *C. glutamicum* by complementing two missing enzymes, diacylglycerol acyltransferase (DGAT) and phosphatidic acid phosphatase (PAP), by expressing the *atf1* and *atf2* genes encoding DGAT from the native TAG producer *Rhodococcus opacus* and the *pgpB* gene encoding PAP from *E. coli*. In addition, to increase the fatty-acyl-CoA availability for lipid synthesis, *tesA* encoding thioesterase to form free fatty acid from fatty acyl-ACP and *fadD* encoding acyl-CoA synthetase, both derived from *E. coli* were expressed. TAGs could only be detected by the additional deletion of four cellular lipase genes and one diacylglycerol kinase gene, indicating that inactivation of lipase activity is crucial for lipid accumulation in *C. glutamicum*. Moreover, the deletion of *fasR* to derepress fatty acid biosynthetic genes and thereby to enhance fatty acid synthesis and the blockage of the acetate and lactate formation has a strong synergistic effect on TAG production (3.7-fold increase in the fatty acid content). The final strain achieved a 7.5% yield of total fatty acids from glucose (2.4 g/L intracellular fatty acids and 0.6 g/L extracellular fatty acids) in shake flasks, which corresponded to fatty acid content of 17.8% of the dry cell. This result demonstrated the potential of *C. glutamicum* as a lipid producer (Table 1) (Plassmeier et al. 2016).

Production of other value-added compounds

Recently, Tsuge et al. reported on production of shinorine, an ultraviolet-absorbing mycosporine-like amino acid useful in cosmetics and skin care to prevent UV-induced skin damage, by metabolically engineered *C. glutamicum* (Tsuge et al. 2018). They constructed a shinorine-producing strain by expressing a shinorine biosynthetic operon from the actinobacterium *Actinosynnema mirum* constituting four genes responsible for shinorine biosynthesis from sedoheptulose-7-phosphate (S7P), an intermediate of the pentose phosphate pathway. Thus, shinorine biosynthesis requires a distinct pentose phosphate pathway precursor from that for most aromatic compounds, namely, E4P formed in the same pathway. To allow for the accumulation of the precursor S7P, modification of the pentose phosphate pathway was performed, namely, deletion of *tal* gene encoding transaldolase and overexpression of *gnd* gene encoding 6-phosphogluconate dehydrogenase. This modification improved shinorine production from gluconic acid to 19.1 mg/L, that is 8.3-fold higher compared to the value exhibited by the parent strain without metabolic pathway modification (2.3 mg/L) (Table 1) (Tsuge et al. 2018). Such a strategy for increasing S7P would be applicable to other chemicals derived from this compound.

Conclusions and outlooks

Driven by the progress of metabolic engineering technologies, the portfolio of chemical products that can be produced by microbial fermentation from renewable resources has been extensively expanded. However, the productivity of most of bio-based value-added chemicals, e.g., aromatic compounds, isoprenoids, and advanced biofuels, remains at low level even at the stage confirming the proof of concept that is not applicable to commercial production. In this regard, engineered *C. glutamicum*, which achieved markedly high productivity of shikimate, 4-HBA, and 4-ABA at a commercially applicable level, can serve as a promising platform to produce such valuable chemicals from renewable sugars in an environmentally compatible bioprocess. However, further improvement of producer strains would be needed to enhance the cost-competitiveness of bio-derived aromatic chemicals to conventional petroleum- or plant-derived chemicals. One of key challenges would be improvement of the product yield. For microbial aromatic production, aerobic reaction condition is required for their efficient synthesis, because in their production, NADH formed via glycolysis must be reoxidized by

respiration to keep redox balance. However, the aerobic reaction condition typically promotes carbon flux into the TCA cycle that accompanies formation of a large amount of CO_2 as a major byproduct (at 30–50% as carbon yield) (Kogure et al. 2016). In this respect, cofactor engineering of key metabolic enzyme(s) (e.g., converting the cofactor preference of shikimate dehydrogenase from NADPH to NADH) would have potential to enable efficient aromatic production with high yield under microaerobic or even under anaerobic conditions like the case of organic acid production by *C. glutamicum* (Inui et al. 2004; Okino et al. 2005). This is based on the improvement of redox balance under anaerobic conditions as is demonstrated in L-valine production by engineered *C. glutamicum* (Hasegawa et al. 2012). Reduction of the carbon flux to the byproduct-forming pathways like TCA cycle by inactivating or reducing the activity of key enzymes, e.g., pyruvate kinase or citrate synthase, preferably in product-production phase-specific manner, represents an another possible approach to improve product yield (Kallscheuer and Marienhagen 2018; Noda et al. 2016).

Recent development of multi-omics analysis and advanced computer-assisted metabolic analysis technologies enabled rational and systematic metabolic engineering of microbial hosts to enhance productivity and yield of the target compound to the theoretical maximum, instead of the classical intuitive metabolic engineering. Such technologies include metabolic analysis based on the precise genome-scale metabolic model specialized for a particular organism, as well as molecular dynamics simulation of mRNA and protein structure, which enables optimization of pathway gene expression and improvement of the key enzyme function (Isa et al. 2018). These approaches in a synergistic way would contribute to remove metabolic bottlenecks and to design most appropriate metabolic pathways from genome-wide perspectives. Another important issue to address to realize industrial bioproduction is an enhancement of robustness and tolerance of a microbial host toward stressed conditions due to severe product toxicity and/or high osmotic pressure that would limit the productivity. In the case of shikimate production by engineered *C. glutamicum*, the tendency of the engineered strains to aggregate presumably due to impaired cell surface integrity represents another critical issue to address for large-scale production. To overcome these issues, evolutionary or mutational approaches to obtain strains with desired phenotype and following specification of responsible mutations would help rational engineering of robust strains with enhanced stress tolerance and/or improved cell integrity (Buschke et al. 2013; Lessmeier and Wendisch 2015; Mahr et al. 2015; Oide et al. 2015). Such efforts would further explore the full potential of *C. glutamicum* as a platform biocatalyst for production of various valuable chemicals from renewable feedstocks, opening the door to the sustainable and eco-friendly bio-industry that replaces the conventional petrochemical industry.

Availability of supporting data No supporting data are provided.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of 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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