Endophytes: the novel sources for plant terpenoid biosynthesis

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Abstract
Terpenoids are natural compounds predominantly present in plants. They have many pharmaceutical and/or nutritional functions, and have been widely applied in medical, food, and cosmetics industries. Recently, terpenoids have been used in the clinical treatment of COVID-19 due to the good antiviral activities. The increasing demand for terpenoids in international markets poses a serious threat to many plant species. For environmentally sustainable development, microbial cell factories have been utilized as the promising platform to produce terpenoids. Nevertheless, the bioproduction of most terpenoids cannot meet commercial requirements due to the low cost-benefit ratio until now. The biosynthetic potential of endophytes has gained attention in recent decades owing to the continual discovery of endophytes capable of synthesizing plant bioactive compounds. Accordingly, endophytes could be alternative sources of terpenoid-producing strains or terpenoid synthetic genes. In this review, we summarized the research progress describing the main and supporting roles of endophytes in terpenoid biosynthesis and biotransformation, and discussed the current problems and challenges which may prevent the further exploitation. This review will improve our understanding of endophyte resources for terpenoid production in industry in the future.

Key points
- The mechanisms employed by endophytes in terpenoid synthesis in vivo and in vitro.
- Endophytes have the commercial potentials in terpenoid bioproduction and biotransformation.
- Synthetic biology and multiomics will improve terpenoid bioproduction in engineered cell factories.

Keywords Endophyte · Terpenoid · Biosynthesis · Biotransformation · Microbial cell factory

Introduction
Terpenoids, also referred to as isoprenoids, are a large family of the most abundant natural products in nature derived from isoprene units. They exist in almost every organism, but are mainly synthesized by plants as secondary metabolites. To date, more than 80,000 terpenoids have been identified, some of which have important medicinal, physiological, metabolic, communication, and defense functions, and are widely utilized in food, cosmetics, and pharmaceutical industries (Pichersky and Raguso 2018). Especially, terpenoids exert their effects on human health including anticancer, antiviral, anti-inflammation, immune regulation, antioxidation, and other functions (Davies et al. 2015; Hill and Connolly 2020). Due to the good antiviral effects (such as SARS-CoV-2 and hepatitis C virus) (Chao et al. 2016), many terpenoids have been used in the clinical treatment of COVID-19 (Bailly and Vergoten 2020; Murck 2020).

As shown in Fig. 1, isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), the fundamental structural units of all terpenoids, are synthesized through the mevalonate (MVA) pathway and the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway. IPP and DMAPP can be reversibly isomerized by isopentenyl pyrophosphate
Plant endophytes as the alternative sources for terpenoid bioproduction

Plant endophytes are a group of microorganisms that colonize in plant tissues without apparently pathogenic effects to their hosts. Researchers have indicated the presence of one or more types of endophytes in every plant studied to date (Gupta et al. 2020; Shi et al. 2015; Shi et al. 2016). The population of endophytes in a plant is highly variable and depends on various components, including plant genotype, plant growth stage, plant physiological status, the type of plant tissues, the environmental condition of the soil, and different agricultural practices (Gupta et al. 2020). Endophytes exhibit complex interactions with their hosts. For example, they are known to enhance plant growth and nutrient gain, and to improve the tolerances of plants to various types of abiotic and biotic stresses. In addition, it has been proved that endophytes were able to produce some plant-derived high-value compounds, including terpenoids or their precursors (Kharwar et al. 2011; Kusari et al. 2013; Kusari et al. 2014a; Newman 2018; Souza et al. 2011). Over the past decades, many valuable terpenoids with antioxidant, anticancer, and antimicrobial activities have been successfully identified from endophytes (Table 1).

Why could endophytes produce so many phytochemicals like terpenoids and other compounds, while the microbes isolated from other habitats were seldomly able to do so? Some studies considered that the phytochemical biosynthesis functions of endophytes were obtained through their long-term evolution in their hosts by the horizontal gene transfer between plant-associated endophytes and the hosts, as well as among the endophytes (Tiwari and Bae 2020; Zhang et al. 2019), making endophytes as important sources of diverse plant secondary metabolites. In contrast, some other studies showed that the secondary metabolite biosynthetic genes in some endophytes were not homologous with their hosts, and some genes were even absent in the host genomes (Heinig et al. 2013), indicating that the phytochemical-producing endophytes might evolve independently. Therefore, some systematic studies are needed to elucidate why endophytes could produce plant secondary metabolites.
Heterologous production of endophyte-derived terpenoids

Although various terpenoids can be synthesized by endophytes, all of these endophytes have not been suitable for commercial application due to the low yield and the weakening biosynthetic capacity upon repeated subcultivation. Development of techniques in metabolic engineering and synthetic biology promoted the idea of expressing the terpenoid biosynthetic pathway in industrial microbes (Belcher et al. 2020). Besides, system biology techniques enlarged the bank of potential genes involved in terpenoid biosynthesis from environments. For example, modern metagenomic sequencing approaches and de novo assembly of microbial genomes from metagenome data provide powerful strategies in discovering the novel microbes and genes involved in terpenoid biosynthesis from the endosphere and rhizosphere microorganisms, regardless of whether the microbes are culture-dependent or culture-independent (Carrión et al. 2019).

Here, by taking Huperzine A (HupA) as an example, we discuss the feasibility of heterologous production of endophyte-derived terpenoids. HupA is a sesquiterpene alkaloid naturally existing in members of the Huperziaceae, such as Huperzia serrata. A large number of clinical trials have shown that HupA is an effective therapeutic medicine with
minor side effects for Alzheimer’s disease (AD) due to its high anti-acetylcholinesterase activity (Zhao et al. 2013). So far, part biosynthetic pathway of HupA in the family Huperziaceae has been illustrated (Fig. 2a). The first two steps are catalyzed by lysine decarboxylase (LDC) and copper amine oxidase (CAO), which convert L-lysine to 5-amino-3-pentanal, the precursor of HupA. The genes expressing LDCs and CAOs have been identified from Lycopodium clavatum (Bunsupa et al. 2016) and H. serrata (Xu et al. 2017), but their enzymatic promiscuity activities were strong. Many other enzymes participating in the HupA biosynthetic pathway remain to be identified.

The discovery of HupA biosynthetic genes from endophytes related to family Huperziaceae is of great value for both scientific research and commercial applications. In 2010, two HupA-producing endophytic fungi Shiraia sp. Sf114 (Zhu et al. 2010) and Cladosporium cladosporioides LF70 (Zhang et al. 2011) were isolated from the leaves of H. serrata, and their yields of HupA were 142.6 μg/g and 39.61 μg/g dry mycelium, respectively. Afterwards, Zhu and colleagues sequenced the whole genome of Shiraia sp. Sf114, identified a putative HupA biosynthetic gene cluster (Yang et al. 2014), and then heterogeneously expressed the ScCAO gene of the gene cluster into Escherichia coli (Yang et al. 2016). They found that the genetically modified E. coli strain was able to convert cadaverine to 5-amino-3-pentanal. In 2014, another HupA-producing fungal endophyte Colletotrichum gloeosporioides ES026 was isolated from H. serrata with the HupA yield of 45.81 μg/g dry mycelium at most (Zhao et al. 2013). Shu and colleagues did de novo RNA sequencing of C. gloeosporioides ES026 and genes encoding LDC (CgLDC) and CAO (CgCAO) were identified (Zhang et al. 2015). Later on, they heterogeneously overexpressed CgLDC and CgCAO in E. coli, and successfully obtained 5-amino-3-pentanal in cells (Zhang et al. 2017) (Fig. 2b).

Besides HupA, the microbial-based production of some other terpenoids was supported by genetic information of endophytes. For example, John M. Gladden and colleagues discovered 26 putative terpene synthases (TPSs) derived from four endophytic fungal strains (Daldinia eschscholzii EC12, Hypoxylon sp. CO27, Hypoxylon sp. CI4A, and Hypoxylon sp. EC38), of which 12 were functionally expressed in E. coli and induced the production of a wide variety of monoterpenoids and sesquiterpenoids (Wu et al. 2016). Liu and colleagues first identified and described a chimeric diterpene synthase from the endophyte C. gloeosporioides ES026 as (5R,12R,14S)-dolasta-1(15),8-diene synthase (CgDS), the chimeric fungal clade II-D terpene synthases and catalyzes a C1-III-IV cyclization, and obtained this compound with the titer of 7.3 mg/L in S. cerevisiae (Bian et al. 2018). Zhan and colleagues isolated an endophytic bacterium Pseudomonas sp. 102515 that could produce zeaxanthin diglucoside, a promising antioxidant terpenoid that belongs to the family of carotenoids, from the leaves of Taxus chinensis, and then amplified a carotenoid biosynthetic gene cluster of this strain in Pseudomonas putida KT2440, resulting in the yield of zeaxanthin diglucoside at 121 mg/L (Fidan and Zhan 2019).

Although it is technically available to express endophyte-derived terpenoid biosynthetic genes in engineered strains, it seems that the yield of terpenoids is still short of the commercial expectations. It is expected that further improvement of terpenoid production can be achieved through metabolic engineering combined with protein engineering.

**Endophytes with the ability to enhance their hosts’ terpenoid production**

Endophytes could not only produce terpenoids by themselves, but also stimulate the terpenoid accumulation in their host plants. For example, tanshinones, a golden group of diterpene quinones with the pharmacological effects, like antitumor, antioxidation, anti-inflammation, cardiovascular and cerebrovascular protection, are the major lipophilic ingredients of Salvia miltiorrhiza Bunge (Danshen) (Dong et al. 2011). To date, people have identified more than 40 tanshinones from the chemical constituents of S. miltiorrhiza, such as tanshinone I-VI, cryptotanshinone, isotanshinone I-II, and danshenol A, but their biosynthetic pathways in S. miltiorrhiza are only partially elucidated (Guo et al. 2016) (Fig. 3). In 2012, a tanshinone-producing endophytic fungus Trichoderma atroviride D16 was isolated from S. miltiorrhiza root, which can produce tanshinones I and IIA in rich mycological medium (Ming et al. 2012). One year later, Qin and colleagues found that T. atroviride D16 could promote the cell growth and tanshinone production in S. miltiorrhiza hairy roots, through the transcriptional regulation by the polysaccharide fraction (PSF) secreted from T. atroviride mycelium (Ming et al. 2013). According to further analysis via infrared (IR) and nuclear magnetic resonance (NMR), the key components in PSF responding for boosting tanshinone production were mannose, glucose, and galactose (Wu et al. 2019). According to the proteomics analysis of the S. miltiorrhiza hairy roots exposed to PSF, the tanshinone biosynthesis induced by PSF in S. miltiorrhiza hairy roots may be correlated with peroxide reaction, Ca2+ triggering, jasmonic acid (JA) signal transduction, and protein phosphorylation, finally resulting in an increase of leucine-rich repeat (LRR) protein synthesis (Peng et al. 2019). Another endophytic fungus Chaetomium globosum D38 isolated from the roots of S. miltiorrhiza induced its host to produce more tanshinones, especially for dihydrotanshinone I and cryptotanshinone, through upregulating the expression of key genes involved in tanshinone biosynthetic pathway (Zhai et al. 2018).

There are some other examples to show how endophytes promote the terpenoid production in their hosts. Alok Kalra
and colleagues isolated a few nitrogen-fixing root-associated and indole-3-acetic acid (IAA)–producing endophytes from different parts of the medicinal plant *Withania somnifera*, and found that they could induce their hosts to produce more withaferin-A in roots, one of the major phytochemical triterpenoid derivatives in *W. somnifera*, by inducing IAA production and increasing the transcriptional activity of withanolide biosynthesis genes in roots, especially MEP-pathway genes (*DXS* and *DXR*) (Pandey et al. 2018). Zhang and colleagues screened out an endophytic bacteria *Bacillus pumilus* from the medicinal herb *Glycyrrhiza uralensis* Fisch. They found that *B. pumilus* can improve *G. uralensis* growth under drought stress through the modification of antioxidant accumulation and enhance glycyrrhizic acid content by the incremental expression of key enzymes, such as squalene synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and beta-amyrin synthase (Xie et al. 2019).

In summary, cells or fragments of endophytes could play the role of elicitors to induce the formation of bioactive compounds, such as terpenoids, in plant or cell suspension cultures. This endophyte-induced bioactive compound synthesis in plant cells is considered through the signal transduction process, which is composed of several steps including recognition of elicitors, signal transduction, integration with transcription factors, and gene activation (Zhai et al. 2017). In detail, endophytic elicitors, such as fungal proteins, oligosaccharides, and polyunsaturated fatty acids (Wu et al. 2019), could activate the signal transduction pathways in plants, including ion fluxes and Ca^{2+} signaling pathway, nitric oxide (NO) signaling pathway, reactive oxygen species (ROS) signaling pathway, salicylic acid (SA) signaling pathway, JA signaling pathway, and their cross-talking. Then, the produced signal molecules could integrate with transcription factors which regulate the expression of bioactive compound–associated functional genes (Zhao et al. 2005), leading to the significant accumulation of bioactive compounds in plant cells (Fig. 4).

Although the outline of endophyte-induced plant terpenoid synthesis has made important progress, the detailed mechanisms are not declared yet. For example, how the various signaling molecules regulate the expression of transcription factors during the endophyte-induced accumulation of terpenoids in medical plants is scarcely investigated. Han and colleagues proved that class I TGA transcription factors combined with methyl jasmonate could increase the production of triptolide and two sesquiterpene pyridine alkaloids, but the detailed mechanism has not been revealed (Han et al. 2020). Moreover, novel endophyte-derived elicitors, signal molecules, transduction pathways, transcriptional factors linking with in situ terpenoid metabolism, and the docking

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**Fig. 2** The biosynthetic pathway of HupA. **a** The proposed biosynthetic pathway of HupA in members of the Huperziaceae. **b** The heterogeneous expression of HupA synthetic genes from endophytes in microbial cell factory. LDC, lysine decarboxylase; CAO, copper amine oxidase. Solid arrows indicate the established relationships, and dashed arrows indicate hypothetical relationships.
processes between elicitors and the corresponding receptors are not elaborated. Benefiting from the technological development in synthetic biology and botany, plant synthetic biology is regarded as another hot spot (Nemhauser and Torii 2016). Nonetheless, the development of plant synthetic biology is still at an initial stage due to the insufficiency of quantificationally standardized components and incompatibilities between standardized components and plant system (Patron et al. 2015). In the future, researchers should focus on the studies of the key transcription factors related to the endophytic elicitors. Only when key transcription factors screened out can they be transferred to the corresponding...
medical plants or other model plants to increase the accumulation of the secondary metabolites greatly. In addition, despite that a variety of synthetic sensors has been used in the study of plant endogenous signaling pathways, complex genetic circuits have not been realized in plants. So future plant synthetic biology development depends on a large degree of basic research breakthrough.

**Biotransformation of terpenoids by endophytes**

Besides the function of terpenoid biosynthesis directly or indirectly, endophytes have the potential with the function of terpenoid decoration to change their structures and bioactivities. Currently, some endophytes have been utilized to produce useful enzymes, which have significant regio- and stereo-selectivities, for the production of terpenoid derivatives (Corrêa et al. 2014).

Ginseng is an important pharmaceutical herb belonging to Araliaceae family. It has been utilized in Chinese medicine for thousands of years. Ginsenosides are the most valuable and major active triterpenoids in ginseng species with the therapeutic effects of anti-tumor, anti-age, and hepatitis therapeutic effectiveness. The biosynthetic pathway of ginsenosides has been elucidated (Wang et al. 2020) (Fig. 5a). They are composed of major ginsenosides (Rb1, Rb2, Rc, Rd, Rg1, etc.) and rare ginsenosides (Rg3, Rh1, Rh2, F2, compound K, etc.). Compared with major ginsenosides, rare ginsenosides (deglycosylated ginsenosides) are more pharmaceutically active, because they have relatively smaller sizes and are easily able to penetrate cell membranes (Xu et al. 2003). Considering that rare ginsenosides are too few to be purified from most natural ginseng plants, it is of great significance to study the conversion of major ginsenosides into rare ginsenosides (He et al. 2019). It was found that ginsenoside Rb1, the main active ingredient of *Panax Notoginseng*, could be deglycosylated to form ginsenoside F2 and compound K by the glucosidase of the endophytes *Fusarium* sp. YMF1.02670 and YMF1.02193 (Luo et al. 2013) (Fig. 5b). Yin and colleagues screened out 32 β-glucosidase-producing endophytes from *Platycodon grandiflorum*, among which *Luteibacter* sp. JG09 can effectively convert ginsenosides Rb1, Rb2, Rc, and Rd into rare ginsenosides F2 and compound K, and convert ginsenoside Rg1 into rare ginsenoside Rh1 (Cui et al. 2016) (Fig. 5b). The maximum production rate of ginsenosides F2 and compound K reached 94.53% and 66.34%, respectively. Later on, they successfully isolated another β-glucosidase-producing endophytic bacterium *Burkholderia* sp. GE 17-7 from *P. ginseng* roots with the capability of converting ginsenoside Rg3 from Rd1 (Fu et al. 2017) (Fig. 5b). Accordingly, further studies to identify and modify various β-glucosidases from endophytes have the potential to effectively increase ginsenoside bioproduction.

Endophytes have potential biotransformation activities on many other terpenoids. For example, ursolic acid is a pentacyclic triterpenoid with the anti-inflammatory, anti-

![Fig. 4](image-url)
Fig. 5 The proposed biosynthetic pathway of ginsenosides. 

**a** Key enzymes and intermediates involved in ginsenoside biosynthesis. 
- SS, squalene synthase; SE, squalene epoxidase; DDS, dammarenediol-II synthase; PPDS, protopanaxadiol synthase; PPTS, protopanaxatriol synthase; CYP450, cytochrome P450 monooxygenase; UGT, uridine diphosphate glycosyltransferase. Green compounds represent major ginsenosides; blue compounds represent rare ginsenosides.

**b** Examples of biotransformation of ginsenosides by endophytes. 
- *Fusarium* sp. YMI 02630, *Fusarium* sp. YMI 02193, *Luteibacter* sp. JG09, *Burkholderia* sp. GE 17-7.
microbial, and antiviral activities. Some of its derivatives are very important for the structure-activity relationship study, but they are hard to be obtained through the chemical modification of ursolic acid since ursolic acid has limited active sites. Thanks to the investigation on endophytes, the fungal endophytes isolated from H. serrata, Pestalotiopsis microspera, and Umbelopsis isabellina were reported to be able to transform ursolic acid to new compounds by structural modification through maybe the cooperation of transferases and esterases (Fu et al. 2011a, b). A second example is on the gentiopicroside (GPS), a monoterpenoid glucoside whose pharmacological properties could be activated after the enzymatic or acidic hydrolysis (Zeng et al. 2014). An endophytic fungus Penicillium crustosum 2T01Y01, isolated from a medicinal plant Dendrobium candidum Wall. ex Lindl., had a high GPS-transforming ability, and could produce three known and four novel deglycosylated GPSs (Zeng et al. 2014). It was proposed that the GPS metabolic pathways in P. crustosum 2T01Y01 mainly include deglycosylation, hydrolyzation, cyclization, reduction and hydrogenation, or oxidation and decarboxylation. The authors speculated that the deglycosylation by the β-glucosidase existing in the fungus might be the initiation step, but the enzymes involved in the other steps need to be elucidated.

In summary, endophytes can be efficiently used for the biotransformation of natural compounds through their special enzymes. The biotransformation reactions mainly include hydroxylation, hydrolysis, reduction, oxidation, epoxidation, O-methylation, ring-expansion, isomerization, and methyl migration reactions. Considering that rational design and directed evolution of enzymes could accelerate the improvement of their specificities, stabilities, and/or efficiencies, these strategies could be used to ultimately improve the conversion efficiencies of biotransformational enzymes in the future.

Conclusions and future perspectives

Endophytes are a treasure trove of terpenoid biosynthesis through direct or indirect manners. Nevertheless, investigations on endophyte-related terpenoid synthesis are still in their infancy. To achieve their commercial applications in industries, several serious challenges should be overcome. Firstly, the lifestyles and genetic systems of most endophytes are poorly understood, which have hampered our in vivo genetic manipulations. Secondly, the heterologous expression of endophyte-derived genes within the normal microbial cell factories is usually in face with instability, low enzymatic activities, misfolding, incorrect post-translational modification, a mass of crosstalk between the endogenously primary metabolism and the artificial metabolic pathways, and so on (Kusari et al. 2014b). Thirdly, if the target endophytes prefer to make steady functions in plant-associated microbiomes through physical and/or metabolic interactions, their in vitro monocultures might be in face with the gradual reduction in terpenoid yields. With the development of the multi-omics approaches and bioinformatics, exploring, identifying, and characterizing the genetic and metabolic elements involved in the terpenoid synthesis in endophytes have been advancing. With further development and the combination of enzyme engineering, pathway optimization, molecular techniques, and some other modern technologies, endophytic-derived terpenoid bioproduction could be boosted furthermore.

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