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Review article

Advances in biosynthesis, regulation, and metabolic engineering of plant specialized terpenoids

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ABSTRACT

Plant specialized terpenoids are natural products that have no obvious role in growth and development, but play many important functional roles to improve the plant's overall fitness. Besides, plant specialized terpenoids have immense value to humans due to their applications in fragrance, flavor, cosmetic, and biofuel industries. Understanding the fundamental aspects involved in the biosynthesis and regulation of these high-value molecules in plants not only paves the path to enhance plant traits, but also facilitates homologous or heterologous engineering for overproduction of target molecules of importance. Recent developments in functional genomics and high-throughput analytical techniques have led to unraveling of several novel aspects involved in the biosynthesis and regulation of plant specialized terpenoids. The knowledge thus derived has been successfully utilized to produce target specialized terpenoids of plant origin in homologous or heterologous host systems by metabolic engineering and synthetic biology approaches. Here, we provide an overview and highlights on advances related to the biosynthetic steps, regulation, and metabolic engineering of plant specialized terpenoids.

1. Introduction

Plants produce an array of diverse metabolites that are either essential (primary metabolites) or non-vital (secondary or specialized metabolites) for the central processes of growth and development. Among such metabolites, terpenes or terpenoids constitute a large and structurally diverse class of compounds with more than 80,000 entities reported so far from different living organisms including plants [1]. While terpenes are hydrocarbons based on combinations of the C_5 isoprene units, terpenoids are compounds related to terpenes that may have additional functional groups. However, both the terms are often used interchangeably. Plants produce both primary terpenoid metabolites (such as sterols, carotenoids, many hormones) and secondary or specialized terpenoid metabolites with vast majority of them belonging to specialized metabolites. The specialized terpenoids represent the most diverse and the largest group of plant specialized metabolites and are often specific or unique to individual plant species or groups of species. Specialized terpenoids provide overall fitness to the plant

Abbreviations: AACT, acetoacetyl-CoA thiolase; AcAc-CoA, acetoacetyl-CoA; CAS, cycloartenol synthase; CCD, carotenoid cleavage deoxygenase; ChPP, chrysanthemyl diphosphate; CMK, 4-(cytidine 5-diphospho)-2-*C*-methyl-D-erythritol kinase; CPT, *cis*-prenyltransferase; DIMBOA, 24-dihydroxy-7-methoxy-1,4-benzoxazin-3-one; DMAPP, dimethylallyl diphosphate; DMNT, 48-dimethylnona-1,3,7-triene; DXP, 1-deoxy-D-xylulose-5-phosphate; DXR, 1-deoxy-D-xylulose-5-phosphate reductoisomerase; DXS, 1-deoxy-D-xylulose-5-phosphate synthase; FPP, farnesyl pyrophosphate; FPPS, FPP synthase; G3P, glyceraldehyde 3-phosphate; G8H, geraniol-8-hydoxylase; GA, gibberellins; GES, geraniol synthase; GFPP, geranylfarnesyl diphosphate; GFPPS, GFPP synthase; GGPP, geranylgeranyl diphosphate; GGPPS, GGPP synthase; GGPPSL, GGPPS-like; GP, geranyl monophosphate; GPP, geranyl diphosphate; GPPS, GPP synthase; GRP, GGPPS recruiting protein; HDR, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate reductase; HDS, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate synthase; HMBPP, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-Coenzyme A; HMGR, HMG-CoA reductase; HMGS, 3-hydroxy-3-methylglutaryl-Coenzyme A synthase; IP, isopentenyl phosphate; IPK, IP kinase; IPP, isopentenyl diphosphate; IPPI, IPP isomerase; IspS, isoprene synthase; LPP, lavandulyl diphosphate; MCT, 2-*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase; MDS, 2-*C*-methyl-D-erythritol 24-cyclodiphosphate synthase; MEP, 2-*C*-methylerythritol 4-phosphate; MK, mevalonate kinase; MVA, mevalonic acid; MVAP, mevalonate 5-phosphate; MVAPP, mevalonate diphosphate; MDD, mevalonate diphosphate decarboxylase; NCED, 9-*cis*-epoxycarotenoid dioxygenase; NNPP, nerylneryl diphosphate; NNPPS, NNPP synthase; NPP, neryl diphosphate; NPPS, NPP synthase; OSC, oxidosqualene cyclase; PMK, phosphomevalonate kinase; SQE, squalene epoxidase; SQS, squalene synthase; TMTT, 48,12-trimethyltrideca-1,3,7,11-tetraene; TPS, terpene synthase; UDP, uridine diphosphate; UGTs, uridine diphosphate glucosyltransferases

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through their roles in the interaction of plants with their environment. They play important roles in direct and indirect plant defense against herbivores and pathogens, in reproduction by attraction of pollinators and seed disseminators, and in plant thermo-tolerance [2,3]. Unlike primary terpenoid metabolites (for example: sterols, pigments, phytohormones, and ubiquinone) that are produced ubiquitously, specialized terpenoids are produced in a species-, tissue-, organ-, and response-specific manner. All terpenes are derived from the universal 5-carbon precursors, which are formed via two different pathways located in different subcellular compartments. Terpenes are classified according to the number of five-carbon units present in their chemical structure. They are hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di- (C_{20}), sester- (C_{25}), tri- (C_{30}), and tetra- (C_{40}) terpenes [4,5]. The basic backbone structures of all terpenes are formed by the action of terpene synthases (TPSs), encoded by a mid-size family of genes. Subsequently, the basic terpene structures undergo various enzymatic modifications such as hydroxylation, dehydrogenation, acylation or glycosylation, resulting in a myriad of chemically diverse terpenoid compounds [5]. However, compounds having deviations to the general 5n carbon backbone such as homoterpenes (C_{11} and C_{16}) derived from sesquiterpenes and diterpenes, and sterols and steroids ($C_{27\text{-}29}$) originated from triterpenoids are also called as terpenoids [6,7]. Reports indicate that these modifications are sometimes associated with gene clusters in which TPS gene is clustered with genes encoding modifying enzymes. The knowledge derived from the understanding of biosynthesis and regulation has been applied for engineering the homologous or heterologous systems for higher production of specialized terpenoids to enhance the plant trait or for industrial application. This review provides an overview and highlights on the recent developments on various biosynthetic and regulatory aspects involved in specialized terpenoid metabolism in plants. Further, significant advances in metabolic engineering for production of specialized terpenoids in different platforms are summarized.

2. Formation of basic building blocks of terpenoids

Despite their large structural diversity, all terpenoids are synthesized from the universal five carbon precursors, isopentenyl diphosphate (IPP) and its allylic isomer dimethylallyl diphosphate (DMAPP). In plants, these precursors are derived from two alternate and independent biosynthetic pathways localized in different subcellular compartments. While the classical mevalonic-acid (MVA) pathway gives rise to IPP starting from acetyl-CoA in the cytosol, 2-*C*-methylerythritol 4-phosphate (MEP) pathway leads to the formation of IPP and DMAPP from pyruvate and glyceraldehyde-3-phosphate in the plastids (Fig. 1) [2].

The MVA pathway encompasses six enzymatic steps involving acetoacetyl-CoA (AcAc-CoA) thiolase (AACT), 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) synthase (HMGS), HMG-CoA reductase (HMGR), mevalonate kinase (MK), phosphomevalonate kinase (PMK), and mevalonate diphosphate decarboxylase (MVD or PPMD) [8,9]. These enzymes sequentially convert acetyl CoA into AcAc-CoA, HMG-CoA, mevalonic acid (MVA), mevalonate 5-phosphate (MVAP), mevalonate diphosphate (MVAPP), and IPP, respectively. MVA pathway is generally known as cytosolic with enzymes located in the cytosol or associated with the ER (e.g. HMGR) (Fig. 1) [10]. However, localization of MVA pathway enzymes in other subcellular compartments has been reported. While AACT has been shown to be localized in cytosol, ER, and peroxisomes, downstream enzymes of MVA pathway MK, PMK, and MVD have been found in peroxisomes [11–14]. IPP isomerase (IPPI) involved in isomerization of IPP to DMAPP and *vice versa* was shown to have peroxisomal, plastidial, and mitochondrial localization [15]. Despite these above-mentioned evidences, further studies in terms of presence of possible transporters of terpenoid precursors between the compartments (especially between peroxisomes and cytosol) are required to ascertain the differential localization of MVA pathway enzymes.

The MEP comprises seven enzymatic steps that include 1-deoxy-D-xylulose-5-phosphate (DXP) synthase (DXS), DXP reductoisomerase (DXR), 2-*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase (MCT), 4-(cytidine 5-diphospho)-2-*C*-methyl-Derythritol kinase (CMK), 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MDS), (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate synthase (HDS), and (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate reductase (HDR) [16]. The pathway starts with the condensation of pyruvate and glyceraldehyde 3-phosphate (G3P) to form DXP by DXS. DXP is converted to (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP) by the sequential action of DXR, MCT, CMK, MDS, and HDS. HDR catalyzes the last step of MEP pathway in which HMBPP is simultaneously converted into IPP and DMAPP (Fig. 1) [2,8]. It is well established that enzymes of MEP pathway are encoded by the nuclear genome and imported into plastids, where they show sub-plastidial localization so as to facilitate the production of specific types of terpenoids [17,18].

The five-carbon units formed via the cytosolic MVA pathway serve as precursors mainly for the biosynthesis of sesquiterpenoids, polyprenols, phytosterols, brassinosteroids, and triterpenoids, and for terpenoid biosynthesis in mitochondria (e.g., ubiquinones, polyprenols). Whereas IPP and DMAPP derived from the plastidial MEP pathway are preferably used in the formation of hemi-, mono-, di-, sester-, tetraterpenoids (carotenoids and their breakdown products), phytohormones such as cytokinins and gibberellins, chlorophyll, tocopherols, and plastoquinones (Fig. 1) [8]. Though MVA and MEP pathways operate independently in different subcellular compartments, metabolic cross-talk between the two pathways has been reported (Figs. 1) [2,18]. The extent of the cross talk remains, however, unclear and further studies are needed to provide evidence on the metabolic fate of and MVA- and MEP- derived IPP and DMAPP.

Until recently, IPP and DMAPP were believed to be generated in plants through classical MVA and MEP pathway enzymes. However, it was shown that plant genomes encode another IPP generating protein, isopentenyl phosphate kinase (IPK) [19,20]. It was shown that IPK localizes to the cytoplasm, where it transforms isopentenyl phosphate (IP) and possibly dimethylallyl phosphate (DMAP) to IPP and DMAPP via ATP-dependent phosphorylation (Fig. 1). All sequenced plant genomes showed the presence of genes encoding IPK indicating its possible role in modulating the ratios of IP to IPP and DMAP to DMAPP and thus serving an unknown role in regulating terpenoid biosynthesis [20]. Research in *Arabidopsis* revealed that IP and possibly DMAP originate from the active dephosphorylation of IPP (DMAPP) by dedicated two-domain (hydrolase/peptidase) members of the Nudix hydrolase superfamily (AtNudx1 and AtNudx3) that, together with IPK, coordinately regulate the concentration of IPP destined for higher order terpenoid biosynthesis (Fig. 1) [21]. Investigations on IPK and Nudix hydrolases in other plant species could shed further insights into the role of these novel enzymes in plant terpenoid metabolism. Nevertheless, the knowledge derived thus far in IPK and Nudix hydrolases can be exploited as novel strategy for high-level production of commercially important terpenoids.

3. Biosynthesis of prenyl diphosphate intermediates

The C_5 basic building blocks IPP and DMAPP formed through cytosolic MVA and plastidial MEP pathways, are fused in a “head-to-tail” manner by the catalytic activity of short-chain prenyltransferases (prenyl diphosphate synthases) located in both compartments to form linear prenyl diphosphates, which serve as central precursors of all terpenoids (Fig. 1). The C_{10} geranyl diphosphate (GPP), which serves as precursor for all regular monoterpenoids, is formed by a head-to-tail condensation of IPP and DMAPP catalysed by the plastid localized enzyme GPP synthase (GPPS) (Fig. 1) [2]. GPPSs characterized so far from different plant species exist as either homodimeric or heterodimeric structures composed of two identical sub-units or one small sub-unit

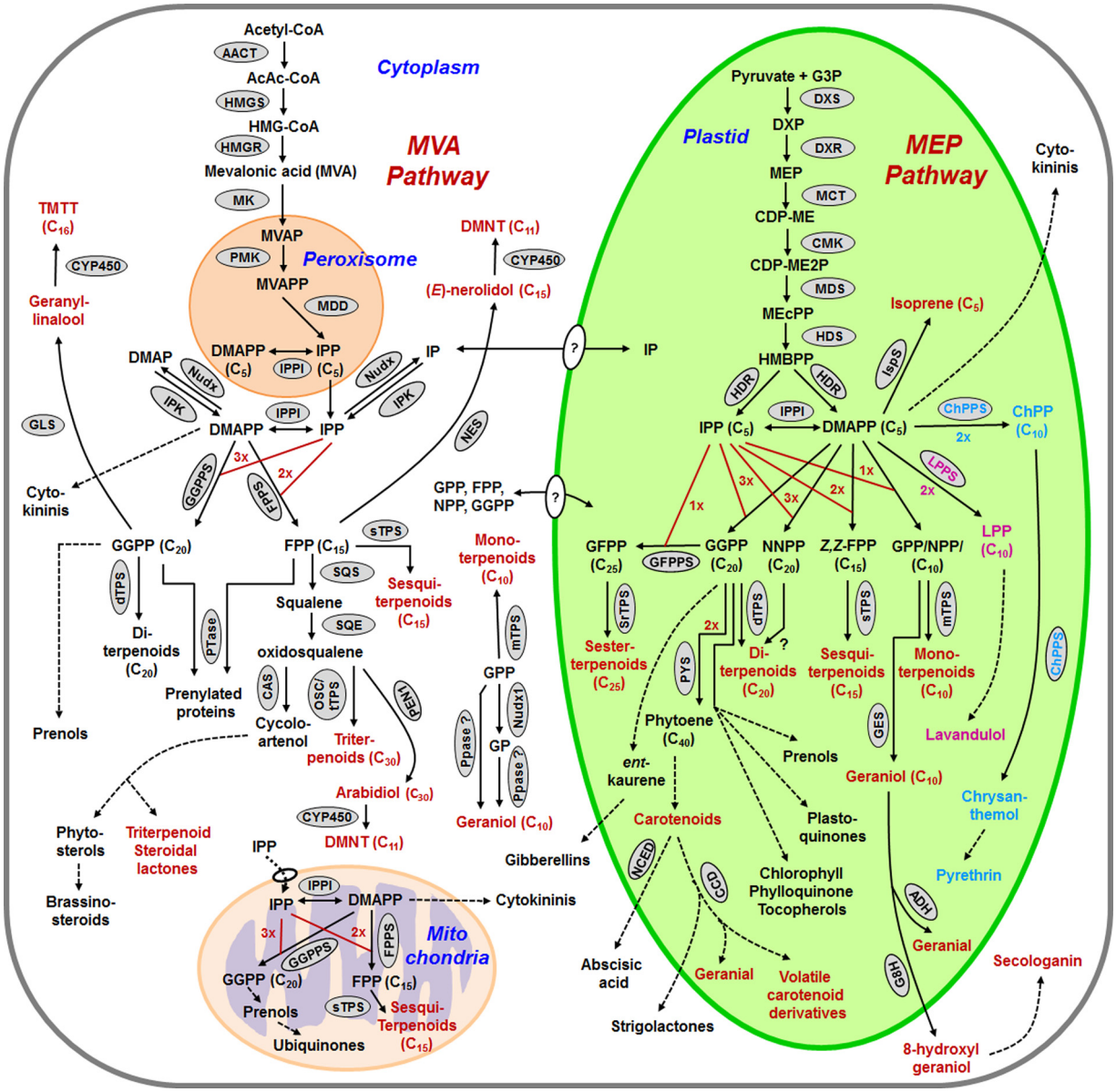

Fig. 1. Schematic overview of terpenoid biosynthesis in plants.

Enzymes are marked by grey ovals. Solid and dashed arrows indicate single and multiple enzymatic steps, respectively. Abbreviations: AACT, acetoacetyl-CoA thiolase; AcAc-CoA, acetoacetyl-CoA; CAS, cycloartenol synthase; CDP-ME, 4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol; CDP-ME2P, 4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol phosphate; ChPP, chrysanthemyl diphosphate; ChPPS, chrysanthemyl diphosphate synthase; CMK, CDP-ME kinase; DMAPP, dimethylallyl diphosphate; DMNT, 4,8-dimethylnona-1,3,7-triene; dTPS, diterpene synthase; DXP, 1-deoxy-D-xylulose 5-phosphate; DXR, DXP reductoisomerase; DXS, DXP synthase; FPP, farnesyl diphosphate; FPPS, farnesyl diphosphate synthase; G3P, glyceraldehyde-3-phosphate; G8H, geraniol-8-hydroxylase; GES, geraniol synthase; GFPP, geranylfarnesyl diphosphate; GFPPS, geranylfarnesyl diphosphate synthase; GLS, geranyllinalool synthase; GP, geranyl phosphate; GPP, geranyl diphosphate; GPPS, geranyl diphosphate synthase GGPP, geranyl geranyl diphosphate; GGPPS, geranyl geranyl diphosphate synthase; HDR, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate reductase; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGS, HMG-CoA synthase; HMBPP, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate, HMGR; HDS, (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate synthase; IPPI, isopentenyl diphosphate isomerase; IP, isopentenyl phosphate; IPK, isopentenyl phosphate kinase; IPP, isopentenyl diphosphate; IspS, isoprene synthase; LPP, lavandulyl diphosphate ; LPPS, lavandulyl diphosphate synthase ; MCT, 2-*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase; MDS, 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase; MEP, 2-*C*-methyl-D-erythritol 4-phosphate; MEcPP, 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate; MK, mevalonate kinase; MPDC, mevalonate diphosphate decarboxylase; mTPS, monoterpene synthase; MVAP, mevalonate 5-phosphate ; MVAPP, mevalonate 5-diphosphate; PMK, phosphomevalonate kinase; NCED, 9-*cis*-epoxycarotenoid dioxygenase; NPP, neryldiphosphate; NPPS, neryldiphosphate synthase; NNPP, nerylneryl diphosphate; NNPPS, nerylneryl diphosphate synthase; OSC, oxidosqualene cyclase; PPase, pyrophosphatase; pTase, prenytransferase; PYS, phytoene synthase; SQS, squalene synthase; SQE, squalene epoxidase, sTPS, sesqiterpene synthase; SrTPS, sesterterpene synthase; TMTT, 4,8,12-trimethyl-trideca-1,3,7,11-tetraene.

(SSU) with one large sub-unit (LSU), respectively. All homodimeric GPPSs and the LSU of heterodimeric GPPSs (GDS_LSU) possess two aspartate-rich DD(X)2–4D, with the exception of a GPPS from orchid *Phalaenopsis bellina* [22]. Though most homomeric GPPSs characterized to date produce GPP as the main product, PaIDS1 from *P. abies* and CrGGPPS1 from *C. roseus* were shown to have bifunctional geranyl and geranylgeranyl diphosphate synthase [G(G)PPS] activity, capable of forming both GPP and GGPP in substantial amounts [23,24]. The heteromeric GPPSs have been reported in angiosperms that produce large amounts of monoterpenoids. Structurally, the heteromeric GPPS

consists of a non-catalytic small subunit (SSU-I) and a large subunit (LSU), which could be either inactive or function as GGPPS / G(G)PPS on its own and interaction between the two subunits results in an active heteromeric GPPS [24]. Two conserved CxxxC motifs (where "x" can be alanine, leucine, isoleucine, valine, glycine, serine or methionine) present in all SSUs and one conserved CxxxC motif in all LSUs and GGDS are crucial for the interaction between SSU and LSU/GGPPS [25,26]. Further, a separate lineage of SSU (SSU II) genes encoding GGPS-related proteins (GGR) was identified in *Arabidopsis* GGR also contained two conserved CxxxC motifs that are essential for the interaction with LSU [26]. GGR, like SSU-I proteins, modified the chain length of the product and also accelerated the GPPS activity of the LSU [25].

Besides GPP, neryl diphosphate (C_{10}; NPP, a cisoid isomer of GPP) formed by head-to-tail coupling of IPP and DMAPP by a plastidial *Z*-prenyltransferase, neryl diphosphate synthase (NPPS1/SlCPT1), was shown to be the precursor for regular monoterpenoids in glandular trichomes of cultivated tomato (*Solanum lycopersicum*) [27,28]. Whereas, the non–head-to-tail condensation of two DMAPP units to lavandulyl diphosphate (C_{10}; LPP) and chrysanthemyl diphosphate (C_{10}; ChPP), is catalyzed by LPP synthase (LPPS) and ChPP synthase (ChPPS), respectively [29,30]. While GPP and NPP serve as precursors for regular monoterpenes, LPP and ChPP act as intermediates in the formation of irregular monoterpenoids lavandulol and pyrethtrin, respectively (Fig. 1).

The C_{15} farnesyl diphosphate (FPP), formed from the condensation of one DMAPP and two IPP molecules catalyzed by the enzyme FPP synthase (FPPS), serves as the natural precursor of sesquiterpenoids, triterpenoids, and sterols. FPPSs have been characterized from several plant species and contain two aspartate-rich DD(X)2–4D motifs (where "X" represents any amino acid) that are essential for prenyl–substrate binding [31]. FPPSs are known to be cytosolic enzymes; however, isozymes of different size generated due to differential transcriptional initiation are localized to the cytosol or the mitochondria where they provide FPP pools for the formation of cytosolic and mitochondrial terpenoids, respectively [32]. Though peroxisomal localization of FPPS was shown based on YFP fusion experiments in *C. roseus* cells, no peroxisomal targeting was observed for fluorescent FPPS fusion proteins in *Arabidopsis* consistent with proteomic studies of the cytosol and purified peroxisomes [33–35]. It was generally accepted that FPP in *trans* (*E*) configuration served as precursor for all sesquiterpenoids, however, the *cis* prenyl diphosphate *Z,Z*-FPP that is formed from IPP and DMAPP by a plastid localized *Z,Z*-farnesyl diphosphate synthase (zFPPS), was shown to be involved in the formation of class II sesquiterpenoids in trichomes of *S. habrochaites* [36]. Similarly, another *cis*-prenyltransferase (SlCPT6) from *S. lycopersicum* having plastidial localization catalyzed *Z,Z*-FPP formation from NPP (Fig. 1) [27].

Geranylgeranyl diphosphate (GGPP, C_{20}) is formed by the condensation of three molecules of IPP and one molecule of DMAPP by the enzyme GGPP synthase (GGPPS). GGPP serves as the entry point leading to the biosynthesis of diverse group of primary and secondary terpenoid compounds. These compounds include the plastid-derived carotenoids and their derivatives (abscisic acid and strigolactones), chlorophylls and its hydrolysis product phytol (used for producing tocopherols and fatty acid phytyl esters), tocopherols, gibberellins, plastoquinones, polyprenols, diterpenoids, and mitochondria-derived polyterpenes [37–39]. Recently, a salvage pathway was shown to be important for phylloquinone biosynthesis where in chlorophyll hydrolysis releases phytol (C_{20}), which is further phosphorylated [39].

Consistent with the location of these diverse pathways, various GGPPS isoforms encoded by a multigene family and localized in different subcellular compartments have been reported in plants (Fig. 1) [37]. As mentioned earlier, GGPPS is also known to function as large subunit (LSU) of heterodimeric GPPS or as bifunctional G(G)PPS in some plants [2,23,24]. In *Arabidopsis*, one of the GGPPS isozymes, AtGGPPS11, functions as a hub protein that interacts with PSY and GGR thereby channeling GGPP toward carotenoids and chlorophylls biosynthesis, respectively [40]. In addition, a plastid localized nerylneryl diphosphate (NNPP) synthase (NNPPS or SlCPT2) forming NNPP, an isomer of GGPP, was reported in tomato (Fig. 1) [28]. Recently, a novel mechanism directing metabolic flux toward a specific product in the terpenoid metabolic network was demonstrated in rice. It was discovered that GGPPS recruiting protein (GRP) belonging to SSU-II subfamily, forms a heterodimer with the only plastidic GGPPS (OsGGPPS1), thus controlling GGPPS dimerization state and catalytic properties. By interacting with GGPPS, GRP changed its localization from stroma to thylakoid membranes, where the heterodimer existed in a complex with chlorophyll biosynthetic proteins [41].

Geranylfarnesyl diphosphate (GFPP, C_{25}) is a *trans* prenyl diphosphate and is the precursor for sesterterpenoids biosynthesis. GFPP is formed from condensation of one DMAPP and four IPP molecules by the action of GFPP synthase (GFPPS) (Fig. 1). Though GFPPSs were identified in a few prokaryotes and archaeon, the first report of GFPPS isolation and characterization was recently reported from *Arabidopsis* [42–44]. Four geranylgeranyl pyrophosphate synthase-like (GGPPSL) proteins (AtGGPPSL6, 7, 9, and 10) catalyzed the conversion of IPP and DMAPP into GFPP [45]. In the same year, another GFPPS was reported that was isolated from the glandular trichomes of the Mint species *Leucosceptrum canum*. Phylogenetic analysis suggested that GFPPS may have evolved from plant GGPPSs under the influence of positive selection [46].

4. Formation of terpenes by terpene synthases

Following the formation of different linear C_{5n} prenyl diphosphate precursors, an array of structurally diverse linear or cyclic terpene olefins or terpene alcohols is generated by the action of TPSs (Fig. 1) [47]. TPSs are encoded by a mid-sized gene family with 30–100 members per plant and are evolved from ancestral triterpene synthase- and prenyltransferase–type enzymes through repeated events of gene duplication and subsequent loss, gain, or fusion of protein domains and further functional diversification [5,48,49]. The huge structural diversity of terpenoids is mainly due to the reorganization of the basic carbon skeletons initiated either by the leaving of the pyrophosphate or by the protonation of a carbon–carbon double bond carried out by class I and class II TPSs, respectively [50]. While Class I TPSs have Asp-rich substrate binding DDxx (D,E) motif and metal binding NSE/DTE motif, Class II TPSs have a DxDD motif. These characteristic motifs are highly conserved and dominant for their functions. While hemi-(C_5), mono-(C_{10}), sesqui- (C_{15}), di-(C_{20}), and sester-(C_{25}) terpenes are known to be synthesized from prenyl-pyrophosphates by both Class I and II TPSs, most of the tri-(C_{30}) and tetra-(C_{40}) terpenes are synthesized by only class II TPSs from "head-to-head" type precursors [50]. It is known that some TPSs can accept several prenyl diphosphates (e.g. GPP and FPP) while others are specific to a particular prenyl diphosphate [47,50]. The carbocation intermediate formed by Class I and II TPSs undergoes further conversions, leading to the formation of several products by a single promiscuous enzyme [4,51]. Further, the plant TPS superfamily has been divided into seven clades (TPSa, b, c, d, e/f, g and h) based on sequence relatedness and functional assessment. Among them, clade-a/-b/-g, clade-d, and clade-h are unique to angiosperms, gymnosperms, and lower land plants, respectively [5]. The class I TPSs are mainly represented by mono-TPSs (gymnosperm TPS-d, angiosperm TPS-b), sesqui-TPSs (gymnosperm TPS-d, angiosperm TPS-a), and diTPS (gymnosperm TPS-d, angiosperms TPS-e/f), whereas class II and bifunctional class I/II TPSs are represented by the TPS-c clade [5,49,52].

4.1. Hemiterpenes

Hemiterpenes are the smallest and simplest terpenes having C_5 structure. Isoprene is the best known hemiterpene and is emitted from the leaves of many trees (including conifers, poplars, oaks, and willows)

and herbs (e.g., *Hamamelis japonica*) [53,54]. Isoprene acts as a signaling and defense molecule and has been an important platform in the synthetic chemistry industry for the synthesis of rubber, pharmaceuticals, flavors, and potential biofuels [55]. Isoprene is synthesized by isoprene synthase (IspS) belonging to class I TPS and TPS-b subfamily which converts DMAPP into isoprene. Recent studies in *Arabidopsis* suggested that IspSs are most likely originated by parallel evolution from monoterpene synthases of TPS-b subfamily [57]. Genes encoding IspS have been isolated and characterized from several plants such as kudzu, poplar, aspen, velvet bean, willow, and oak [54–56]. Other known hemiterpenoids found in plants are tiglic, angelic and isovaleric, acids. Utililactone and epiutililactone are two chlorinated hemiterpenes present in the leaves of *Prinsepia utilis* are known to have immunosuppressive activity, whereas pubescenoside A reported from *Ilex pubescens* possess anti-platelate aggression activity [58].

4.2. Monoterpenes

Monoterpenes are C_{10} acyclic or monocyclic compounds produced from GPP. Monoterpenes are well known for their strong odor and aromatic properties acting as major constituents of essential oils of aromatics plants that are widely used in the cosmetic, perfume, food, and pharmaceutical industries [53,59]. They also possess properties to empower plants in dealing with the biotic and/or abiotic stresses [8,60]. Menthol, limonene, geraniol, linalool, eucalyptol, borneol, and camphor are some of the important representatives of monoterpenoids. Monoterpenes are generally formed from GPP by the action of monoterpene synthases (mTPSs), which belong to TPS-b, d1 or g subfamilies (Fig. 1) [60]. The reaction mechanism for all mTPSs involves carbocationic reaction initiated by the divalent metal (usually Mg^{2+} or Mn^{2+}) ion-dependent ionization of the substrate. The resulting cationic intermediate further undergoes a series of cyclizations, hydride shifts or other rearrangements until the reaction is terminated by proton loss or the addition of a nucleophile [51]. Many mTPSs form single products from the substrate whereas several reports of mTPSs forming multiple product from the same substrate are also present. For example, a promiscuous mTPS, *Cs*TPS2FN, isolated from *Cannabis sativa* encodes the formation of (+)-α-pinene, (+)-β-pinene, myrcene, (-)-limonene, and β-phellandrene [59]. In contrast, the recombinant proteins AaTPS2 from *Artemisia annua* and MkTPS1 from *Murraya koenigii* produced a single product, β–myrcene and -(-)sabinene, respectively [60,61]. In some cases, simple monoterpenes formed from GPP by a mTPS could undergo several transformations leading to a different end product. For instance, (-)-(4*S*)-limonene formed by limonene synthase undergoes several transformations by various enzymes located in different subcellular compartments leading to the formation of menthol [62]. Similarly, geraniol formed by geraniol synthase serves as the precursor for iridoids biosynthesis in some plants like *C. roseus* [63,64]. Though most monoterpenoids reported so far are synthesized from the classical substrate GPP, some mTPSs use NPP (*Z* isomer of GPP) to form monoterpenoids. It was recently shown in cultivated tomato (*Solanum lycopersicum*) that glandular trichomes-specific NPPS1/SlCPT1, a plastidial *Z*-prenyltransferase, was able to use IPP and DMAPP to generate NPP that acts as substrate for the biosynthesis of monoterpenes [6,28]. In Tagetus cinerariifolium plastid localized ChPPS functions as a bifunctional enzyme with ChPPS and chrysanthemol synthase activities and forms chrysanthemol, precursor of pyrethrins (Fig. 1) [65]. The lengths of mTPSs range between 600 and 650 amino acids and possess N-terminal transit peptide required for plastidial localization [66]. However, there are exceptions to the plastid localization of mTPSs. Dual-function TPSs from cultivated strawberry (*Fragaria ananassa,* FaNES1), snapdragon (*Antirrhinum majus*, AmNES/LIS-1), and sweet basil (*Ocimum basilicum*, ZIS) catalyzing the formation of both mono- and sesqui- terpenoids, have shown cytosolic localization [67–69]. *FaNES2* from cultivated strawberry and *FvNES1* from wild strawberry (F. vesca) were localized to mitochondria and/or plastids [67]. In *Lippia dulcis*, geraniol synthase (LdGES) was shown to be a cytosolic enzyme [70]. The presence of cytosolic mTPSs or bifunctional enzymes raises the question of the origin of their substrates. It is likely that GPP is exported from plastids as several lines of evidence indicate GPP can be exported from plastids to cytosol as no cytosolic GPPS has been reported so far (Fig. 1) [3,69,71]. Despite these evidences to support the transport of GPP for monoterpene biosynthesis, no transporter of GPP has been discovered until now. It is also proposed that GPP could potentially be derived from promiscuous side reactions of FPPS activity in the cytosol [72]. However, the amount of GPP made through this route might not be sufficient to support the biosynthesis of a large quantity of monoterpenes [6].

In addition to the regular biosynthesis of monoterpenes through the involvement of mTPSs, a non-canonical TPS-independent route for monoterpenoid geraniol formation was recently reported in rose (Fig. 1) [73]. Comparison of volatile profiles and differential gene expression of scented and unscented rose cultivars, revealed the role of an unexpected enzyme belonging to a Nudix hydrolase class (RhNUDX1) in geraniol formation in rose petals. RhNUDX1 was localized in the cytosol and exhibited geranyl diphosphate diphosphohydrolase activity by converting GPP into geranyl monophosphate (GP). It was proposed that GP could be further converted to geraniol by an unidentified phosphatase. In addition, the RhNUDX1 enzyme is located in the cytosol, indicating that its substrate, GPP, was obtained either by transport from plastids or via cytosolic generation, but this remains to be solved [73]. Similar to the formation of geraniol via two routes involving either a TPS geraniol synthase or a Nudix, the corresponding aldehyde geranial has also been shown to be formed either though the action of alcohol dehydrogenase or through oxidative cleavage of long chain terpenoid, carotenoid (C_{40}), by carotenoid cleavage dioxygenase (CCD) as described. While geranial was formed from geraniol by alcohol dehydrogenase (ADH) in sweet basil and *Perilla*, it was shown to be produced from the carotenoid lycopene in rice [74–77]. Based on transcriptome analysis, and correlation of gene expression and metabolites content, TPS-independent formation of geraniol by yet to be identified pyrophosphatase (Ppase) and ADH/CCD-dependent formation of geranial was also proposed in aromatic grasses (*Cymbopogon* sp.) (Fig. 1) [78].

4.3. Sesquiterpenes

Sesquiterpenes are a group of C_{15} compounds representing the most prevailing class of terpenes. They are acyclic, monocyclic, bicyclic or tricyclic compounds produced from FPP through the catalytic activity of sesquiterpene synthases (sTPSs), which fall under TPS-a1, a2, d1, d2, d3, e/f or g subfamilies (Fig. 1) [5]. They are constituents of floral scents and also help plants to defend themselves against herbivores and plant pathogens. For instance, sesquiterpenes produced by a tube-specific sTPS get accumulated in the stigma of petunia flowers, before it opens to protect the developing stigma from pathogens [79]. Sesquiterpenoid lactones are chemically distinct compounds from sesquiterpenoids which bears characteristic features as an α-methylene γ-lactone system; α, β-unsaturated carbonyls, or epoxides. Both sesquiterpenoids and sesquiterpenoid lactones show a wide range of biological functions as antimicrobial, anti-inflammatory and antitumor agents [80]. Common sesquiterpenoids are caryophyllene, farnesene, α-humulene, zingiberene, santalenes, and santalols, and the most famous sesquiterpenoid lactones are the antimalarial artemisinin and parthenolide [81]. Conversion of farnesyl pyrophosphate (FPP) to sesquiterpenes by sTPSs employs similar carbocationic based reaction mechanisms as those of mTPSs. However, due to larger carbon skeleton of FPP and the presence of three, instead of two, double bonds increase the structural diversity of the products [51]. In general, the lengths of sTPSs are between 550–580 amino acids and are shorter than mTPSs as they lack transit peptide.

All sesquiterpenes were previously thought to be synthesized

exclusively in the cytosol, using FPP generated via the MVA pathway. However, some reports indicate the formation of small amounts of sesquiterpenes through plastdial FPP pool derived through the promiscuous side reactions of GGPPS [72]. Further, sesquiterpenes in glandular trichomes of wild tomatoes are shown to be synthesized from *Z,Z*-FPP made by a plastidial *Z,Z*-FPPS (Fig. 1) [36]. It was shown in glandular trichomes of wild tomatoes that sTPSs, santalene and bergamotene synthase (SBS), and zingiberene synthase (ZIS) used *Z,Z*-FPP as the substrate to generate a mixture of santalene and bergamotene, and 7-epizingiberene, respectively [82,83]. In addition, there are several reports demonstrating the metabolic cross-talk between MVA and MEP pathway in the biosynthesis of sesquiterpenes [4,84]. For instance, labeling experiments in snapdragon flowers have shown that sesquiterpenes were produced by cytosolic sTPSs using C_5 precursors made in plastids via the MEP pathway [68,85]. In *Stevia rebaudiana* glandular trichomes, both MVA and MEP pathways contribute to the biosynthesis of sesquiterpenes at equal rates [85].

4.4. Diterpenes

Diterpenes encompass chemically heterogeneous group of compounds with a C_{20} hydrocarbon skeleton formed from GGPP. They are classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic, or macrocyclic diterpenes depending on their skeletal core. They participate in primary as well as secondary metabolism of plant. For example, gibberellin (GA) phytohormones and the phytol side chain of chlorophyll participate in plant's primary metabolism, whereas diterpene phytoalexins have been shown to confer resistance against pests or pathogens [86]. So far > 13,000 distinct diterpenes have been reported from plants [87]. Several diterpenoids are used by humans as medicines, fragrances, and flavors. Some of the major commercially used diterpenoids include the anti-cancer drug taxol (paclitaxel) from *Taxus brevifolia,* sclareol from clary *Salvia sclarea* used in fragrance and perfume industries and the natural sweetener steviol from *Stevia rebaudiana* [88–91]. Diterpenes are formed from GGPP originated predominantly from MEP pathway, by the action of diterpene synthases (dTPSs) that belong to TPS-c, d3, e/f, g or h subfamilies (Fig. 1) [5]. Generally, diTPS can be divided into two mechanistically distinct categories: class I and class II enzymes and their lengths are > 200 amino acids longer than mTPSs because of additional conserved internal element [66,92]. The cyclisation of a 20-carbon poly-isoprene diphosphate, usually (*E,E,E*)-GGPP, by one or two TPSs is the committed step in diterpene biosynthesis. The resulting diterpene skeleton is then modified by a series of decorating enzymes, such as CYPP450 s and acyltransferases [87]. While dTPSs are primarily located in plastids, geranyllinalool synthase from *A. thaliana* involved in the biosynthesis of (*E,E*)-geranyllinalool, the precursor of 4,8,12-trimethyltrideca-1,3,7,11-tetraene (TMTT), resides in the cytosol or the ER supporting that its substrate GGPP is present in these compartments (Fig. 1) [6]. Though there has been no *in planta* proof for the presence of cytosolic GGPP, it has been proposed that it could be made either by a cytosolic GGPPS or through export of GGPP into the cytosol made by the plastidial GGPPS (Fig. 1) [93].

4.5. Sesterterpenes

Sesterterpenes are (C_{25}) compounds with five isoprene units and occurs in variety of forms like linear, mono, bi-, tri-, tetra-, and macro cyclic [53]. This subgroup of terpenes consists of rare compounds which are less explored. They play a vital role in host-microbe interactions. In *Arabidopsis thaliana*, lack of two root-specific sesterterpenoids affected the assembly of root microbiota significantly [94].Leucosesterterpenone and leucosterlactone are tertacyclic sesterterpenes and both are potential anti angiogenic agent [54]. Geranylfarnesyl diphosphate (GFPP) made in the plastid by GFPPS is the precursor for sesterterpenes, which are formed by the action of plastid localized sesterterpene synthases (SrTS) (Fig. 1) [6]. STSs follow the same deprotonation/reprotonation sequences of cyclization as that of sTPSs and are often clustered with trans-prenyltransferase GFPPS [95].

4.6. Triterpenes

Triterpenes are C_{30} compounds with six isoprene units as their carbon skeleton. Two FPP molecules derived from MVA pathway fuse 'head-to-head' to generate the linear C_{30} triterpene precursor, squalene, in a reaction catalysed by squalene synthase (SQS) (Fig. 1) [80]. Subsequently, 2,3-oxidosqualene, formed from squalene by squalene epoxidase (SQE), undergoes cyclization to tetra- or pentacyclic structures by specific oxidosqualene cyclases (OSCs)/ triterpene synthases (tTPSs) encoded by multigene families in plants (Fig. 1) [96]. While *A. thaliana* genome contains 13 genes encoding OSCs that make different triterpenes, rice genome has 12 OSC genes [97]. Cycloartenol synthase (CAS) converts 2,3-oxidosqualene to cycloartenol, which acts as the precursor for all sterols that act as the important structural components of membranes and also have roles in signalling (as steroidal hormones) (Fig. 1) [97]. Unlike sterols, triterpenoids are not essential for normal growth and development and exist in plants in simple unmodified form or as triterpene glycosides, which have important functions in plant defense and food quality in crop plants. Besides, they have a wide range of commercial applications in the food, cosmetics, pharmaceutical, and industrial biotechnology sectors [53,97]. More than 20,000 different triterpenoids have been reported so far. Most common example of triterpene saponins modification is three step oxidation at the $C\text{-}_{28}$ position of β-amyrin, α –amyrin, and lupeol, which leads to oleanolic acid (oleanane-type), ursolic acid (ursane-type) and betulinic acid (lupane-type) scaffolds, respectively [98). Triterpene synthases (tTPSs) such as amyrin synthase (AS) and lupeol synthase (LS) that catalyse the formation of simple triterpenes amyrin and lupeol, respectively, have been characterized in many plant species indicating their wide distribution. The simple triterpenes scaffolds are often modified by CYP450 enzymes (e.g., introduction of hydroxyl, ketone, aldehyde, carboxyl, or epoxy groups) to form complex molecules, which further could be acted upon by uridine diphosphate (UDP)-glucosyltransferases (UGTs) to form triterpenoid glycosides, or saponins [97–99]. Another class of compound 4,8-dimethylnona-1,3,7-triene (DMNT), a homoterpene (C_{11}), is reported to be formed by degradation of C_{30} triterpenoid, arabidiol, in roots of *Arabidopsis* (Fig. 1) [6].

In addition to pentacyclic triterpenoids, triterpenoids steroidal lactones such as withanolides derived through sterol pathway have gained attention in recent years due to their medicinal and pharmacological properties. Withanolides are C_{28} steroidal lactones in which C_{22} and C_{26} are oxidized to form lactone ring (Fig. 1) [100]. Withanolides are found mostly in plants from the Solanaceae family that contains more than 600 structurally distinct compounds [101]. The best-known plant to produce withanolides is Withania somnifera, also known in Indian Ayurveda as Ashwagandha, a plant of high repute for thousands of years in Ayurveda [100]. Though not much is known about their biosynthesis, it is clear that the intermediates of the universal sterol pathway act as precursors for the biosynthesis of withanolides. These precursors are proposed to undergo various biochemical transformations like hydroxylation and glycosylation reactions that lead to the formation of various withanolides [101,102].

4.7. Tetraterpenes

Tetraterpenes are C_{40} compounds consisting of eight isoprene units made in plastids. They are derived from phytoene which is formed by a "head-to-head" condensation of two C_{20} GGPP molecules by the action of phytoene synthase (PYS). The most common tetraterpenoids are carotenoids, which are the second most abundant naturally occurring pigments on earth after chlorophylls and as precursor for abscisic acid and strigolactones (Fig. 1) [103]. They are natural fat-soluble pigments

and are either simple unsaturated hydrocarbons having the basic lycopene structure or their corresponding oxygenated analogs, known as xanthophylls [80]. Carotenoids could be either colorless or variations of yellow, orange, and red, and are found in many fruits, flowers, and vegetables. Examples of carotenoids include β-carotene from carrots and sweet potatoes, lycopene found in tomato and watermelon fruits, capsanthin from red peppers, and lutein from marigold flowers. Carotenoids and their derivatives (apocarotenoids) play crucial roles in assembly of photosystems and regulation of growth and development. Apocarotenoids also act as signaling molecules and have roles in plant's interaction with their environment [103]. In humans, carotenoids serve as antioxidants and reduce age-related macular degeneration of the eye, and also are used as dyes and colorants in the food industry [103,104].

5. Diversification of basic terpenes

Following the conversion of linear prenyl diphosphates into linear or cyclic terpene olefins or terpene alcohols by TPSs, the TPS products can further undergo diversification by terpene oxidations carried out by the action of cytochrome P450 oxygenases (CYP450 s), the largest and functionally most versatile enzyme superfamily found in nature, or in some cases by dioxygenases and dehydrogenases. CYP450 enzymes generally catalyze insertion of oxygen (hydroxylation): however, dehydrogenation, isomerization, dimerization, carbon–carbon bond cleavage, reductions, as well as N-, O- and *S*- dealkylations, sulphoxidations, epoxidations, deaminations, desulphurations and several more have been described [105]. CYP450s are classified into families and subfamilies and their nomenclature is provided by nomenclature committee headed by David Nelson [106]. The land plant CYP450 families have been categorized into 11 clans consisting of seven single-family clans (CYP51, CYP74, CYP97, CYP710, CYP711, CYP727, and CYP746), and four multifamily clans (CYP71, CYP72, CYP85, and CYP86) [107]. Even though enzymatic function of many CYP450 s has not been revealed, it has generally been recognized that members of the same family or subfamily catalyze similar reactions or are involved in the same biosynthetic pathway. CYP450 s involved in specialized terpenoid biosynthesis are spread across all 11 families, which are reviewed elsewhere [108,109]. Furthermore, the terpene alcohols and oxidized terpenoids formed by TPSs and CYP450 s can undergo diversification by the addition of acyl, glycosyl, benzoyl, or even alkaloid groups [47].

6. Irregular terpenoids

6.1. Homoterpenes

Homoterpenes, also known as tetra-nor-polyterpenes, are special class of irregular acyclic terpenes that are generated through degradation of regular terpene alcohols. These compounds are among the most widespread volatiles produced and emitted from flowers and from vegetative tissues of angiosperms upon herbivore feeding. They function in attraction of pollinator or natural enemies of herbivorous insects and hence contributing to plant reproduction and defense [6,110]. The two most-studied examples of this group are C_{11} homoterpene 4,8-dimethylnona-1,3,7-triene (DMNT) and the C_{16} homoterpene TMTT, which are respectively derived from sesquiterpenoid nerolidol and diterpenoid geranyllinalool by oxidative degradation catalyzed by CYP450s (Fig. 1) [6,111]. DMNT is formed by the oxidative degradation (*E*)-nerolidol, tertiary sesquiterpene alcohol which is derived from FPP (C_{15}), whereas C_{16} homoterpene TMTT is generated from the oxidative degradation of tertiary diterpene alcohol (*E,E*)-geranyllinalool derived from GGPP (C_{20}) (Fig. 1) [111]. However, it was shown in *A. thaliana* that one P450 enzyme (CYP82G1) was able to catalyze the formation of both DMNT and TMTT compounds from (*E*)-nerolidol and (*E,E*)-geranyllinalool [6,110]. Recent studies in roots of *A. thaliana* suggest that DMNT can also be generated by the oxidative degradation of Arabidiol (C_{30} triterpenoid) catalyzed by another cytochrome P450 monooxygenase, CYP705A1 (At4g15330) [112].

6.2. Carotenoid derivatives or apocarotenoids

Besides homoterpenes, plants produce other irregular terpenoids or apocarotenoids from carotenoids (C_{40}). Apocarotenoids are composed of carbon skeletons with fewer than 40 carbons. They are found in volatiles (e.g., *β*-ionone and *β*-damascenone) and pigments (e.g., safranal, bixin, and β-citraurin) of flowers and fruits [103]. In tomato, cleavage of carotenoids by CCD1 enzymes (SlCCD1A and SlCCD1B) produces various terpenoid volatiles, including neral (*cis*-citral), geranial (*trans*-citral) [113]. The apocarotenoids are formed by the selective oxidative cleavage of carotenoids carried out by carotenoid-cleavage deoxygenases (CCDs), a large family of non-heme iron (II) dependent enzymes. *Arabidopsis* has at least nine members of the gene family that encodes carotenoid cleavage enzymes in which four are CCDs and the remaining five are 9-cis-expoxycarotenoid dioxygenases (NCED). While CCDs are shown to be involved in β-ionone and strigolactone biosynthesis, NCEDs are associated with abscisic acid production [103].

7. Gene clustering in specialized terpenoids metabolism

Presence of gene clusters has been one of the important discoveries in plant metabolism, which has not only accelerated the process of the elucidation of biosynthetic pathways, but also has smoothened the path for metabolic engineering of target specialized metabolites. Gene clustering for several specialized terpenoids biosynthesis has been described in more than 10 plants. Maximum number of gene clustering has been found in the case of triterpenoids and diterpenoids. Till now, about 7 gene clusters for di- and tri- terpenoids, 4 for sesterterpenoids, and 1 each for mono- and sesqui- terpenoids in various plants have been reported (Table 1) [94,95,112,114–125]. Gene clusters involved in thalianol and marneral biosynthesis in *A. thaliana* are the smallest plant metabolic clusters (35–38 kb) characterized so far [122,123]. The first described plant gene cluster was found in *Zea mays* involved in the synthesis of an insect defense compound 2, 4-dihydroxy-7-methoxy-1, 4-benzoxazin-3-one (DIMBOA), a benzoxazinoid [123]. Since then many clusters producing specialized metabolites have been identified. However, the first gene cluster in terpenoid metabolism was reported in diploid oat (*Avena strigosa*) for triterpene avenacin [125]. Metabolic gene clusters so far characterized in terpenoid biosynthesis typically contain TPSs as the first committed step of the biosynthetic pathway, paired with one or more CYP450s from the CYP71 family [124,126]. These two classes of enzymes give rise to diverse number of terpenoid structures that can be further modified by additional enzymes. For example, *O. sativa* contains a gene cluster composed of four TPSs and 6 CYPP450s that produce both phytocassanes and oryzalides [127]. In *Avena strigosa* the triterpene avenacin is produced from a cluster which contains the initial TPS and the cyclase, oxidase, glycosyltransferase and acyltransferase required to convert the terpene precursor into a functional final product [124]. Different research groups have developed *in silico* programs to identify Biosynthetic Gene Clusters (BGCs) in plants such as plantiSMASH, PhytoClust and METACLUSTER [128–130]. It should be noted that though the *in silico* programs have been developed to predict BGCs, recent study suggested that most predicted plant BGCs are not genuine specialized metabolic pathways and argued that BGCs are not a hallmark of plant specialized metabolism [131]. This indicated that BCGs may not occur as frequently as previously thought and that global gene co-expression should be used in parallel to evaluate gene clusters in order to eliminate false positives and to genuinely discover the genetic basis and architecture of plant natural products.

Table 1
List of identified gene clusters in plant specialized terpenoid biosynthesis.

Pathways	Class of compound	Plant species	References
β-phellandrene	Monoterpenoid	*Solanum lycopersicum*	[116]
Capsidiol	Sesquiterpenoid	*Capsicum annuum*	[115]
Lycosantalonol	Dierpenoids	*Solanum lycopersicum*	[116]
Momilactones		*Oryza sativa*	[117]
Oryzalides		*Oryza sativa*	[118]
Phytocassanes		*Oryza sativa*	[119]
Casbene diterpenoids		*Euphorbia peplus*	[120]
Casbene diterpenoids		*Jatropha curcas*	[120]
Casbene diterpenoids		*Ricinus communis*	[120]
(+)-thalianatriene / (−)-retigeranin B / (−)-*ent*-quiannulatene/ (+)-astellatene	Sesterterpenoids	*Arabidopsis thaliana*	[94]
(+)-arathanatriene / (−)-retigeranin B / (−)-*ent*-Quiannulatene / (−)-variculartriene A / (+)-astellatene		*Arabidopsis thaliana*	[95]
(−)-caprutriene		*Capsella rubella*	[95]
(+)-boleracene and (−)-aleurodiscalene A		*Brassica oleracea*	[95]
20-hydroxybetulinic acid	Triterpenoids	*Lotus japonicus*	[121]
Thalianol		*Arabidopsis thaliana*	[122]
Marneral		*Arabidopsis thaliana*	[123]
Tirucalla-7,24-dien-3β-ol		*Arabidopsis thaliana*	[124]
Arabidiol		*Arabidopsis thaliana*	[112]
Cucurbitacins		*Cucumis sativus*	[114]
Avenacins		*Avena strigosa*	[125]

Table 2
Examples of engineering plant specialized terpenoids in microorganisms.

Class	Compound	Titre	Engineered organism	References
Hemiterpenoid	Isoprene	24 g/L	*E. coli*	[163]
Monoterpenoid	Geraniol	1.68 g /L	*S. cerevisiae*	[184]
	1, 8-cineole	653 mg/L	*E. coli*	[175]
	Linalool	505 mg/L	*E. coli*	[175]
Sesquiterpenoid	Amorphadiene	27.4 g/L	*E. coli*	[176]
	Artemisinic acid	25 g/L	*S. cerevisiae*	[182]
	β-farnesene	130 g/L	*S. cerevisiae*	[183]
	Bisabolene	5.2 g/L	*S. cerevisiae*	[185]
	β-farnesene	8.7 g/L	*E. coli*	[177]
Diterpenoid	Geranylgeraniol	3.3 g /L	*S. cerevisiae*	[186]
	Taxadiene	1 g /L	*E. coli*	[178]
	Manoyl oxide	50 mg/L	*C. reinhardtii*	[170]
Triterpenoid	Protopanaxadiol	11.2 g/L	*S. cerevisiae*	[177]
Tetraterpenoids	Lycopene	3.52 g/L	*E. coli*	[179]
	β-carotene	3.2 g/L	*S. cerevisiae*	[187]

8. Regulation of specialized tepenoids biosynthesis

The biosynthesis of specialized terpenoids is tissue- and developmental stage-specific, and also is induced in response to various biotic and abiotic stresses. The spatio-temporal and inducible formation of specialized terpenoids is mostly regulated at the level of transcription via trans-acting factors or transcription factors (TFs) [2]. TFs are DNA-binding proteins that can recognize and bind specific regulatory sequences, the so-called cis-elements, in the promoter of target genes and thus regulate the rate of transcription initiation [132]. Transcription factors can be classified into different families according to their DNA binding domain and there are at least 64 TF families found in vascular plant genomes [133]. TFs that are often capable of coordinating transcription of multiple biosynthetic pathway genes holds great promise for improving the production of target specialized terpenoids, either at the whole-plant level or in culture systems. By manipulating the expression of a single TF, it is possible to affect the expression of several co-ordinately regulated biosynthetic genes, leading to increased metabolite production [134].

Over the last several years, researchers have elucidated the regulatory roles of several genes encoding TFs of WRKY, myeloblastosis (MYB), Basic helix–loop–helix (bHLH), APETALA2/Ethylene-Responsive-Factor (AP2/ERF), jasmonate-responsive ERF (JRE), Basic Leucine Zipper (bZIP), SQUAMOSA promoter-binding protein-like (SPL), and YABBY classes in specialized terpenoids biosynthesis. Among WRKY TFs, those regulating the biosynthesis of monoterpenes in tomato, sesquiterpenoids such as artemisinin in *A. annua*, gossypol in *Gossypium arboretum*, and capsidiol in tobacco, diterpenoids momilactone A in rice, paclitaxel in *Taxus chinensis*, tanshinones in *Salvia miltiorrhiza,* and triterpenoids such as ginsenosides in *Panax quinquefolius* and withanolides in *W. somnifera* have been reported [135–144]. Though MYB TFs are generally known to regulate phenylpropanoids biosynthesis, few reports indicate regulation of both terpenoid and phenylpropanoid biosynthetic pathways. MYB TFs from *Pinus taeda* (PtMYB4) and *Vitis vinifera* (VvMYB5b) influenced the accumulation of terpenoids and phenylpropanoids. SmMYB36 from S. miltiorrhiza inhibits phenolic acids biosynthesis and promotes tanshinone biosynthesis [145]. TFs of bHLH class (TRITERPENE SAPONIN BIOSYNTHESIS ACTIVATING REGULATOR, TSAR1 and TSAR2) were recently shown to regulate triterpenoids biosynthesis in *Medicago truncatula* [146]. In tomato, the AP2/ERF GLYCOALKALOID METABOLISM 9 (GAME9) and a jasmonate-responsive ERF (JRE) regulate steroidal lactones biosynthesis [147,148]. Involvement of AP2/ERFs in transcriptional regulation of sesquiterpenoid biosynthesis in *A. annua* (*AaERF1* and *AaERF2*) and *Zea mays* (*ZmEREB58*), and diterpenoids tanshinone biosynthesis in *S. miltiorrhiza* (SmERF128) has been demonstrated [149–151]. Another AP2/ERF TF (CitERF71) was recently shown to regulate *CitTPS16* expression thereby controlling the production of *E*-geraniol in *Citrus* fruit [152]. In *A. annua* the bZIP transcription factor HY5 interacts with the promoter of the mTPS gene *QH6* in modulating its rhythmic expression [153]. AaSPL2, a SPL class of TF mediates the transcriptional activation of Artemisinic Aldehyde_11 Reductase (*DBR2*) resulting in the improvement on artemisinin content [154]. In spearmint, the TF MsYABBY5 negatively regulates the production of monoterpenes suggesting that it acts as a repressor of secondary metabolism [155].

Besides TFs, role of microRNAs in controlling specialized terpenoids biosynthesis has recently been reported. It was demonstrated that in *A. thaliana*, the miR156-targeted SPLs show a direct and strong regulation on TPS21, which is responsible for the biosynthesis of (E)-β-caryophyllene, a predominant sesquiterpene floral volatile. Further, it was found that miR156-SPLs play a similar role in patchouli in promoting the expression of PatPTS and the production of patchouli oil [156]. Several other miRNAs have been predicted to target genes of specialized terpenoids biosynthesis in different plants. However, experimental proof for the role of these predicted miRNAs is still awaited [157].

In addition, involvement of geranylgeranylation in regulation of specialized tepenoids biosynthesis has been reported in few plants.

Geranylgeranylation is a kind of prenylation (post translational lipid modification) in which a single or dual 20-carbon geranylgeranyl moiety derived from the plastidial MEP pathway is added to one or two cysteines near the C-terminus of target proteins by the enzyme protein geranylgeranyl transferase-I (PGGT) [93,158]. For example, in *Catharanthus roseus,* protein prenylation plays an important role in the jasmonate signaling pathway leading to monoterpene indole alkaloids (MIA) biosynthesis by regulating the expression of MEP and monoterpene secoiridoid pathway genes [159]. A recent study in same plant demonstrated that the plastid-localized GGPPS (CrGGPPS2) plays an important role in MIA biosynthesis through its involvement in providing precursor for protein-geranylgeranyl-transferase (PGGT) involved in regulation modulation of MIA pathway [160]. In *Nicotiana tabacum*, cellulase induced production of a sesquiterpene capsidiol was suppressed by *S*-carvone by interfering with protein prenylation. *S*-carvone inhibited the PTase activity that allows the transfer of the geranylgeranyl group onto the protein involved in the signaling pathway, suggesting that elicitor-induced signaling pathway is regulated by geranylgeranylated proteins [161].

Lately, endophyte-mediated regulation of specialized terpenoids accumulation has been reported in few plants. Endophytes are microorganisms (bacteria and fungi) that reside in plant tissues at inter or intracellular spaces without causing any disease symptoms [162]. They not only assist the plants in their growth by mobilizing nutrients, providing plant growth regulators or protecting them from pathogens, but also regulate the biosynthesis of plant specialized metabolites including terpenoids [163]. It was reported that endophytes enhanced the accumulation of various sesquiterpenoids in *Atractylodes lancea*, diterpenoid forskolin in *Coleus forskohlii*, and triterpenoid withanolides in *W. somnifera* by positively regulating the expression of pathway genes [164–166]. Though the exact mechanism is yet to be discovered, it was proposed that endophyte-plant association may improve production (biomass and specialized terpenoids) by increasing the source (photosynthesis), expanding the sink (glycolysis and tricarboxylic acid cycle), and enhancing the metabolic flux (terpenoids biosynthesis pathway) [167].

9. Metabolic engineering for the production of specialized terpenoids

Besides their role in plant-environment interactions, specialized terpenoids have immense value due to their wide range of commercial and medicinal applications. However, isolation of feasible amounts of these compounds has been hindered owing to low levels of these compounds in their natural sources, slow growth of plants or limitation in cultivating the plant of origin, and the challenges of isolating pure compounds from plant extracts. Moreover, artificial synthesis of these compounds is not feasible or economical due to high degree of structural complexity [168]. Hence, engineering the pathway for target specialized terpenoids in the natural host plants or heterologous plant / microbial production platforms not only provides a means to overcome these obstacles but also facilitates further understanding of the specialized terpenoid biosynthesis. Besides, plant enzyme promiscuity and combinatorial biochemistry can be exploited to synthesize structural scaffolds and functionalizations that are not found in nature. Several recent reviews have covered detailed aspects of different strategies adopted in engineering of specialized terpenoids in microbial and plant systems [169–172]. Some of the successful examples in different systems are discussed here (Table 2).

Microbes, especially *Escherichia coli* and yeast (*Saccharomycescerevisiae*), have been the platforms of choice for engineering plant specialized terpenoids production as they grow fast, do not heavily rely on land/water resources, have capacity to grow on cheap carbon sources, and have well established methods for genetic and metabolic manipulations. *E. coli* has been engineered for production of wide-range of specialized terpenoids including isoprene mono-, (e.g., 1, 8-cineole, linalool), sesqui- (e.g., amorphadiene and β-farnesene), di- (e.g., taxadiene, the precursor for anticancer drug taxol), and tetra- (e.g., lycopene) terpenes [173,174]. Among these engineering examples, production of amorphadiene (27.4 g/L) has been the most successful in terms of yield followed by isoprene (24.0 g/L), β-farnesene (8.7 g/L), lycopene (3.52 g/L), and taxadiene (1.0 g/L) (Table 2) [163,175–179]. Though many terpenoids have been successfully produced to a reasonable level, engineering the production of terpenoid pathway involving plant CYP450 s (due to their membrane localization) has been a great challenge in *E. coli*. Several novel strategies have been reported to overcome this limitation, however, achieving gram quantities of yield is still far from reality [173].

Yeast (*S. cerevisiae*) has been the champion organism used in metabolic engineering of specialized terpenoids. Contrary to *E. coli*, all classes of terpenoids have been engineered in yeast ranging from isoprene, mono-, sesqui-, di-, tri-, and tetra- terpenoids. Production of artemisinic acid, the immediate precursor of antimalarial drug artemisinin, has been the most famous application of yeast in engineering of specialized terpenoids. From production of 1.6 g/L in initial engineering attempts, artemisinic acid production has reached titres of 25 g/L in yeast [180–182]. Further, repurposing of artemisinic acid producing strain has resulted in > 130 g/L of β-farnesene [183]. Other notable examples of terpenoids engineering in yeast are monoterpenes such as geraniol (1.69 g/L), sesquiterpenes like bisabolene (5.2 g/L), diterpenes geranylgeraniol (3.3 g/L), triterpenoid protopanaxadiol (11.02 g/L), and tetraterpenoids like β-carotene (3.2 g/L) (Table 2) [177,184–187]. Yeast, being a eukaryote has an advantage over *E. coli* for engineering of complex terpenoid pathways consisting of plant derived CYP450 s. This has been demonstrated in the case of artemisinic acid production which involved overexpression of CYP450 (*CYP71AV1*), cytochrome P450 oxidoreductase (*CPR1*) and *CYB5* (encoding a cytochrome B5 reductase) from *A. annua* in the MVA engineered *S. cerevisiae* [181]. In addition, yeast has been a highly useful platform for elucidation of different specialized terpenoid pathways involving plant CYP450 enzymes. For instance, pathways for sesquiterpenoids santalols in *Santalum album*, diterpenoid carnosic acid in *Rosmarinus officinalis*, and triterpenoids ginsenosides in *P. ginseng* have been successfully deciphered using yeast system [188–191]. Combinatorial engineering is an emerging application of microbial synthetic biology for drug discovery. Here, enzyme promiscuity is exploited to synthesize novel compounds that are not found in nature. Though some elegant studies have shown the application of combinatorial engineering, further studies are required to achieve the feasible and economical level of production [192,193].

Besides *E. coli* and yeast, photosynthetic microorganisms like Cyanobacteria and *Chlamydomonas reinhardtii* have been explored for engineering different class of terpenoids production [170]. Though there has been considerable progress in metabolic engineering efforts in photosynthetic microbes, the yields of target terpenoids have not been so promising for commercial cultivation. The best yield achieved so far is for the diterpenoid manoyl oxide (50 mg/L) followed by sesquiterpenoids amorphadiene (19.8 mg/L) and bisabolene (11 mg/L), and monoterpenoid limonene (6.7 mg/L) [170]. With the expansion of available hosts and engineering tools along with proper understanding of terpenoid metabolism regulation, enhancement of yield product could be a possibility in near future.

Although, a lot has been done in producing targeted metabolites in microbes, expression of plant derived genes (enzymes) in microbial system has certain restrictions. For example, metabolic engineering of microbes is not possible for terpenoids whose biosynthetic pathway is not completely known. In such a scenario, engineering of host plant (at cell/hairy root culture or whole plant level) or heterologous plant (having similar pathway) is a feasible option. Various strategies have been tried to enhance the production of specialized terpenoids through homologous or heterologous engineering of plants or suspension cultures. Altering the expression of structural gene(s) of specialized

Table 3
Examples of engineering specialized terpenoid metabolism in transgenic cultures or at whole plant level.

Class	Metabolite	Plant	Heterologous/homologous system	Increase in yield	References
Mono-terpenoids	Mentha oil	*M. piperita*	Homologous	2 fold	[198]
	Limonene	*M. piperita*	Homologous	40 fold	[199]
	Geraniol	*N. tabacum*	Heterologous (hairy roots)	204.3 μg/g DW	[200]
	Limonene	*N. tabacum*	Heterologous	10–30 fold	[72]
Sesqui-terpenoids	Artemisinin	*Artemisia annua*	Homologous	2-fold	[201]
	Artemisinic acid	*Artemisia annua*	Homologous	4-11 fold	[149]
	Artemisinin	*N. tabacum*	Heterologous	0.8 mg/g DW	[202]
	Patchoulol and Amorpha-4,11-diene	*N. tabacum*	Heterologous	1,000-fold	[72]
Di-terpenoids	Tanshinones	*Salvia miltiorrhiza*	Homologous	87.5 mg/l (about 15-fold)	[203]
	Taxol	*Taxus chinensis*	Homologous	2.7-fold	[197]
Tri-terpenoids	Protopanaxadiol	*N. tabacum*	Heterologous	166.9 μg/g DW	[204]
	Dammarenediol-II	*N. tabacum*	Heterologous	573 μg/g DW	[205]
Tetra-terpenoids	β-carotene	*O. sativa*	Heterologous	23-fold	[206]
	Ketocarotenoids (Astaxanthin)	*O. sativa*	Heterologous	16.23 mg/g DW	[207]

terpenoid pathway or TFs involved in regulation of specialized terpenoid biosynthesis has been widely used. Plant cell suspension or hairy root cultures have served as useful platforms for engineering the production of several specialized terpenoids. In ginseng, overexpression of different triterpenoid pathway genes such as HMGR or SQS in adventitious root cultures has resulted in 2–3 fold enhanced total ginsenosides [194,195]. Similarly, engineering of cell or hairy root cultures by overexpression of single gene or co-expression of more than one pathway genes led to enhanced production (~2 to 5 folds) of diterpenoids such as tanshinones and anticancer molecule taxol [196,197]. Despite such examples of successful engineering, cell or hairy root cultures have serious drawback due to their genetic instability and limited *in vitro* propagation ability for many plant species.

Metabolic engineering at whole plant level is advantageous as the entire pathway or part of the pathway for target specialized terpenoid already exists in the plant and only tinkering of committed, limiting or branch point steps could enhance the production of target metabolites to significant levels. Several reports have demonstrated the improved production of various specialized terpenoids in plants, including mono-, sesqui- di-, tri- and tetra- terpenoids (Table 3) [72,149,197–207]. Engineering of menthol biosynthesis pathway in Peppermint (*Mentha x piperita* L.) was one of the first reports of homologous engineering of specialized terpenoid biosynthesis in which suppression of menthofuran synthase gene resulted in essential oil with less than half of the undesirable (+)-menthofuran in transgenic MFS7A lines [198]. In a subsequent report, it was shown that cosuppression of the limonene hydroxylase gene modified the oil content (up to 80 % of limonene in essential oil compared to 2% in the oil from wild type plants), without influencing the oil yield (Table 3) [199]. Additional engineering of MFS7A lines by overexpression of DXR led to > 50 % increase in essential oil yields with drastically low levels of (+)-menthofuran (≤ 1.9 % of the essential oil) and (+)-pulegone (roughly 0.2 % of the essential oil) [208]. Furthermore, field trials of transgenic Peppermint lines exhibited similar oil yield and composition trends observed in greenhouse-grown lines [208]. Another example of successful homologous engineering of specialized terpenoids is that of *A. annua* in which combined expression of *HMGR*, *FPPS,* and *DBR2* gene resulted in > 3-fold (3.2 % dry weight) enhanced accumulation of artemisinin (Table 3) [202]. These transgenic plants have already been subjected to field trials with an aim to release them for commercial cultivation, which can be a much cheaper source of antimalarial drug. In *C. roseus* transgenic plants, overexpression of bifunctional G(G)PPS, and coexpression of G(G)PPS and GES led to enhancement of iridoid secologanin by ~2-fold and ~3.5-fold without affecting the growth, and these traits were stable in T_1 generation [209]. In the case of heterologous engineering in plants, development of "golden rice" by introducing the genes required for tetraterpenoid β-carotene biosynthesis has been one of the early and famous example [210]. "Golden rice 2" was later developed by introducing much efficient genes of β-carotene pathway resulting in drastic enhancement of β-carotene in [206]. The "golden rice 2" has been since then introduced in several countries. Very recently, carotenoid/ketocarotenoid/astaxanthin biosynthetic pathways were engineered in the endosperm resulting in various types of germplasm, from the yellow-grained β-carotene-enriched Golden Rice to orange-red-grained Canthaxanthin Rice and Astaxanthin Rice, respectively [207].

Homologous or heterologous engineering of specialized terpenoids biosynthesis through transgenic approach has been successful in achieving the desired end product with feasible quantities only in few plant species and with certain pathways. Moreover, homologous engineering in many plant species has been hindered by lack of genetic transformation tools. Furthermore, though microbial platforms have proven to be useful heterologous hosts for engineering and production of several plant specialized terpenoids as discussed before, engineering of pathways for many metabolites has resulted in very low production and needs much efforts in optimization. Lately, *Nicotiana benthamiana* (a wild relative of tobacco) has been explored as synthetic biology platform for producing gram-scale quantities of specialized metabolites including terpenoids. This has been possible because *N. benthamiana* is easily amenable to *Agrobacterium*-mediated transient expression, which allows rapid expression of specialized metabolic pathway genes in a scalable and highly flexible manner [168]. Several important specialized terpenoids belonging to mono-, sesqui-, di-, sester-, and tri- terpenoids class have been produced using this transient approach with sester- and tri- terpenoids showing highest production of 1.13 mg/g DW and 3.3 mg/g DW [168,172].

10. Conclusion

Research over the past few years has witnessed tremendous boost from developments in genomics and metabolomics that has led to better understanding of pathways and regulatory mechanisms involved in the biosynthesis of specialized terpenoids. Studies have revealed presence of noncanonical routes and gene clusters involved in the formation of precursors and also downstream terpenoids in few plant species, adding to the complexities of plant terpenoids biosynthesis. Elucidation of regulatory factors and of gene clusters involved in the biosynthesis of specialized terpenoids in different plant species has provided means for enhancing the biosynthesis of certain specialized terpenoids. Further understanding of precise regulation of already known pathways, less-explored terpenoid catabolism, and identification of newer pathway genes or gene clusters for terpenoids pathways in unexplored medicinally and industrially relevant plants could pave the way to realize enhanced production of terpenoids through *in planta* or heterologous engineering. Though some examples of feasible production of specialized terpenoids in different systems through metabolic engineering or

synthetic biology are available, still many are confined to a collection of elegant engineering demonstrations. Besides, greater research on combinatorial engineering could facilitate production of useful pharmaceutical compounds. The pace in which the research on specialized terpenoids is moving, it is only a matter of time that pathways in different plants are deciphered and feasible amounts of many of the ecologically, medicinally, and industrially relevant molecules is achieved in host plants or in heterologous platforms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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