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Plant specialized metabolism: Diversity of terpene synthases and their products

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Abstract

Terpenoids are ubiquitous to all kingdoms of life and are one of the most diverse groups of compounds, both structurally and functionally. Despite being derived from common precursors, isopentenyl diphosphate and dimethylallyl diphosphate, their exceptional diversity is partly driven by the substrate and product promiscuity of terpene synthases that produce a wide array of terpene skeletons. Plant terpene synthases can be subdivided into different subfamilies based on sequence homology and function. However, in many cases, structural architecture of the enzyme is more essential to product specificity than primary sequence alone, and distantly related terpene synthases can often mediate similar reactions. As such, the focus of this brief review is on some of the recent progress in understanding terpene synthase function and diversity.

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Plant terpene synthases drive metabolic diversity

Terpenoid products are ubiquitous across all kingdoms of life and are among the most structurally and functionally diverse compounds in nature. They are especially widespread in plants where individual terpenoids play key roles both in primary metabolism as photosynthetic pigments, electron acceptors, and hormones, as well as in secondary metabolism, acting as signaling compounds for plant-plant, within-plant, and plant—insect interactions, and as defense compounds [1—4]. Recently, the signaling properties of terpenoids have been further extended by showing their involvement in stigma development via a KARRIKIN INSENSITIVE *2*—mediated signaling pathway [5,*6]. Plant-derived terpenoids have also gained attention for their industrial and medicinal applications [7,8], inflating the value in deciphering the biosynthesis and regulation of these economically relevant compounds. Despite the overwhelming diversity of terpenoid structures, with over 40,000 identified in plants alone [9], they all originate from the same universal 5-carbon building blocks, isopentenyl diphosphate (IPP) and its allylic isomer dimethylallyl diphosphate (DMAPP), which are produced via the plastidial 2*C*-methyl-D-erythritol-4-phosphate (MEP) and extraplastidial mevalonate (MVA) pathways.

The MEP and MVA pathways control flux towards terpenoid products through elaborate multi-faceted regulation that involves primary carbon supply, downstream prenyltransferases (PTs), feedback mechanisms, gene clusters, and formation of biosynthetic enzyme complexes [10]. Upon its synthesis, DMAPP can act as the immediate precursor for hemiterpenes (C_5), like isoprene through isoprene synthase [11], or IPP/DMAPP units can be condensed by PTs to form varyingchain-length prenyl diphosphates [12]. In general, prenyl diphosphates are extended by sequential head-to-tail condensation of 5-carbon units by PTs, resulting in a range of products with increasing chain lengths from geranyl diphosphate (GPP, C_{10}) which yield monoterpenes, to geranylfarnesyl diphosphate (GFPP, C_{25}) for sesterterpenes. In addition, some irregular PT products have been identified as terpenoid precursors formed through non-head-to-tail condensation of IPP and DMAPP [13—15]. Furthermore, a growing number of *cis*-PTs have been identified that form the *cisoid* isomers neryl diphosphate (NPP), *Z,Z*-farnesyl diphosphate (*Z,Z*-FPP), and nerylneryl diphosphate (NNPP) of the typical *trans*-prenyl diphosphates GPP, *E,E*-farnesyl diphosphate (FPP, C_{15}), and geranylgeranyl diphosphate (GGPP, C_{20}), respectively [16].

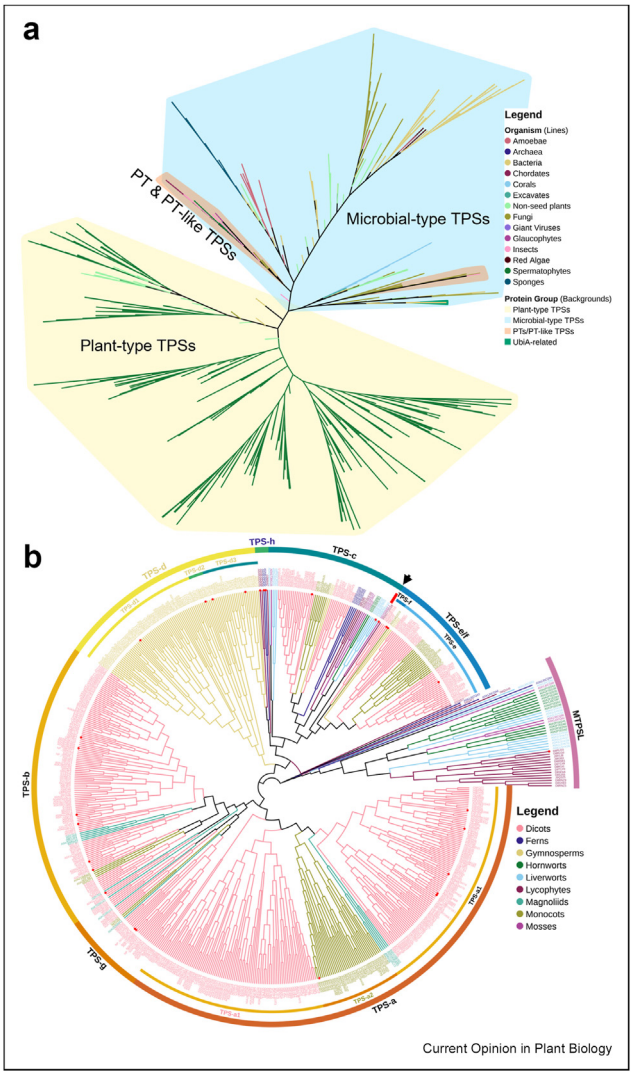
The various chain-length prenyl diphosphates in both *trans* and *cis* conformations are often cyclized or

dephosphorylated by terpene synthases (TPSs) to yield an initial terpene backbone that can be further modified and decorated by downstream enzymes [16,17]. TPSs are enzymes typically responsible for converting a relatively small number of possible substrates into a wide array of structures through what have been considered some of the most complex chemical reactions in nature [18], and their essential role in biology is emphasized by their prevalence in all kingdoms of life with examples in plants [19], bacteria [20], fungi [21], red algae [22], corals [23], sponges [24], insects [25], amoebae [20], and even giant viruses [**26] (Figure 1). Within plants, the spectrum of terpenoids and the corresponding biosynthetic mechanisms forming these compounds are especially complex and diverse [27]. Numerous plant terpenoids are often further modified into more bioactive constituents and stored in specialized compartments to serve physiological and ecological functions, as exemplified by the conversion of sesquiterpenes into sesquiterpene lactones [28], or the formation of acetylated diterpenoids [29]. Such downstream modification of terpenoid skeletons drastically increases the diversity of terpenoid constituents. A single modifying enzyme can utilize one or more terpenoid substrates within a terpenoid biosynthetic network or sequentially modify the same terpenoid compound at different positions to form numerous end products [30,31]. Different groups of TPSs and terpenoid-modifying enzymes have been the subject of several excellent reviews and papers in recent years [27,**32–37]; thus, the focus of this brief review is on recent progress surrounding the structural and functional diversity of select short-chain (C_{10}–C_{25}) TPSs and their products in plants.

Protein architecture and activity separate two TPS classes

Despite the varied activities and primary sequences, all TPSs share a similar tertiary structure composed entirely of α-helices, while having different numbers of α-helical domains [18,38] (Table 1 & Figure 2). The mid-sized family of TPSs can be divided into two main classes based on mechanistic action, rather than sequence similarity, both of which are found in plants [19]. Class I TPSs remove the diphosphate group of a prenyl diphosphate substrate to form an allylic carbocation that can be quenched by water capture or deprotonated, forming either an alcohol or olefin, respectively [18,39]. The prenyl diphosphate substrate is initially coordinated in the active site by a trinuclear divalent metal ion cluster, most often consisting of three Mg^{2+} ions that interact with the aspartate-rich motifs and NSE/DTE conserved amino acid residues, that also facilitates ionization and abstraction of the diphosphate moiety [40–43] (Figure 3). While Mg^{2+} is the typical cofactor tested in vitro, class I TPSs can often utilize other cofactors that may yield distinct product profiles [44–46]. In contrast, class II TPSs are capable of retaining the diphosphate moiety of prenyl diphosphates while cyclizing the prenyl chain through protonation of an olefinic double bond, often generating new substrates for class I TPSs, though class II TPSs can

Figure 1



Phylogenetic relationship between terpene synthases. (**a**) Unrooted phylogenetic tree of short-chain terpene synthases (TPSs) and closely related proteins. Sequences were selected based on references in the text as well as UniProtKB and NCBI databases with an emphasis on plant terpene synthases and the non-seed plant microbial-type TPS-like (MTPSL) proteins. Branches are colored by organism lineage, and shading depicts general groupings of sequences. Protein amino acid sequences were aligned by ClustalW, and a maximum likelihood tree was calculated using MEGA X [105] followed by visualization with TreeViewer [106]. (**b**) Unrooted phylogenetic cladogram of plant short-chain TPSs generated in the same way as in (**a**) from an alignment that excluded non-plant sequences. Branches are colored by plant lineage, while outer lines emphasize TPS subfamilies and the MTPSL group in non-seed plants. The red circles on branch tips indicate proteins mentioned in the text, while the red bar and black arrow highlight the position of *Calohypnum plumiforme* isoprene synthase (CpKSL1/CpISPS) [GenBank: BEH00593.1]. UniProtKB accessions are shown where available; otherwise GenBank and NCBI reference sequence accessions are displayed. PT; prenyltransferase.

Table 1

Plant terpene synthase subfamilies and their typical characteristics.

Subfamily	Plant lineage	Class	Domains	Example[a]	Organism	Main substrate	Main product	Reference
a1	Dicots	I	βα	Q8SA63[c]	*Artemisia annua*	FPP (C_{15})	β-Caryophyllene	[107]
a2	Monocots	I	βα	B2C4D0	*Zea mays*	FPP (C_{15})	β-Caryophyllene	[108]
b	Angiosperms	I	βα	Q40322[c]	*Mentha spicata*	GPP (C_{10})	(−)-Limonene	[109]
c	Mosses	I	βα	BEH00593.1[b]	*Calohypnum plumiforme*	DMAPP (C_5)	Isoprene	[**66]
	Land plants	II	γβα	Q38802[c]	*Arabidopsis thaliana*	GGPP (C_{20})	*ent*-copalyl diphosphate	[110]
	Non-seed plants	II/I	γβα	E3WDE2	*Jungermannia subulata* (liverwort)	GGPP (C_{20})	*ent*-kaurene	[111]
d1	Gymnosperms	I	βα	Q675L1[c]	*Picea abies*	GPP (C_{10})	(−)-Limonene	[112]
d2	Gymnosperms	I	βα	O64405	*Abies grandis*	FPP (C_{15})	γ-Humulene	[113]
d3	Gymnosperms	I	γβα	Q41594	*Taxus brevifolia*	GGPP (C_{20})	Taxa-4(5),11(12)-diene	[114]
		II/I	γβα	Q38710	*Abies grandis*	GGPP (C_{20})	Abietadiene	[115]
e	Land plants	I	γβα	Q39548[c]	*Cucurbita maxima*	CPP (C_{20})	*ent*-kaurene	[116]
		I	βα	G8GJ94	*Salvia sclarea*	8-hydroxy-CPP (C_{20})	Sclareol	[117]
f	Land plants	I	γβα	Q96376	*Clarkia breweri*	GPP (C_{10})	(+)-Linalool	[118]
g	Angiosperms	I	βα	Q84UV0[c]	*Arabidopsis thaliana*	GPP (C_{10})	Linalool	[119]
h	Non-seed plants	I	γβα	A0A8U0DD35	*Phylloglossum drummondii* (lycophyte)	GGPP (C_{20})	Levopimaradiene	[**32]
		II	γβα	A0A8U0DA95[c]	*Osmunda* sp. (fern)	GGPP (C_{20})	8-Endo-copalyl diphosphate	[**32]
		II/I	γβα	A0A8U0DAH5	*Osmunda japonica* (fern)	GGPP (C_{20})	*syn*-manool	[**32]
MTPSL	Non-seed plants	I	α	D8RLD3[c]	*Selaginella moellendorffii* (lycophyte)	FPP (C_{15})	(+)-Germacrene D	[120]

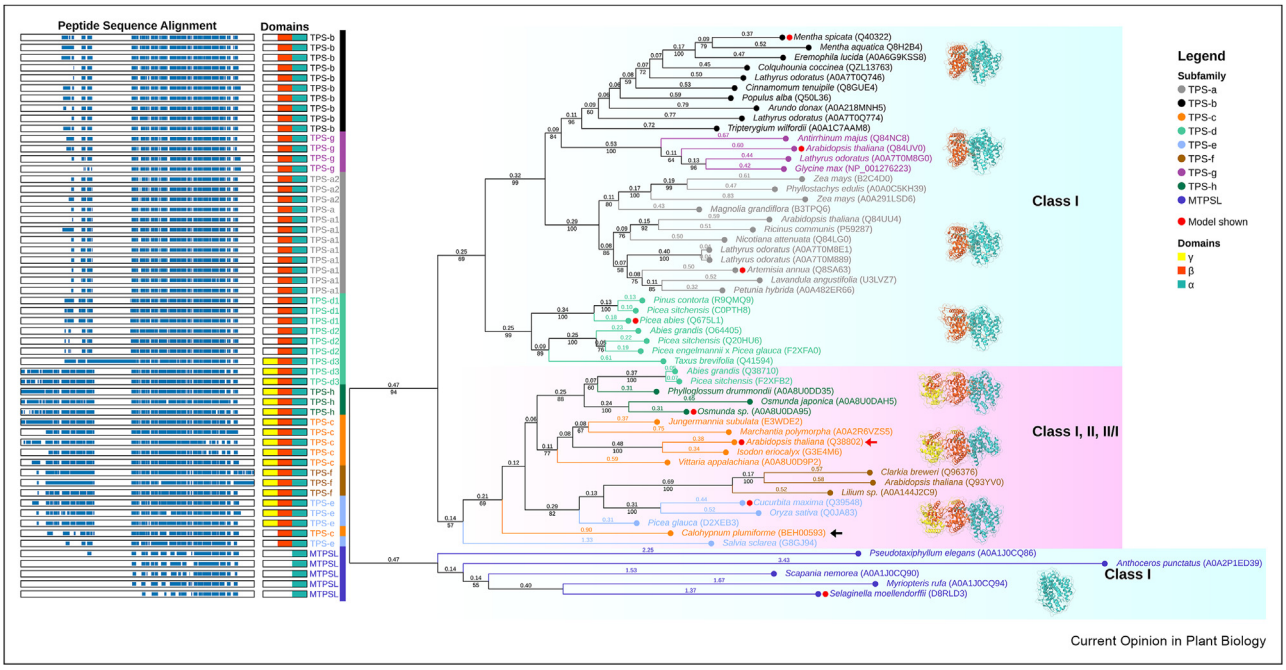
Abbreviations: CPP; copalyl diphosphate, FPP; farnesyl diphosphate, GGPP; geranylgeranyl diphosphate, GPP; geranyl diphosphate.

[a] UniProtKB accession.

[b] GenBank accession.

[c] Structure shown in Figure 2.

Figure 2

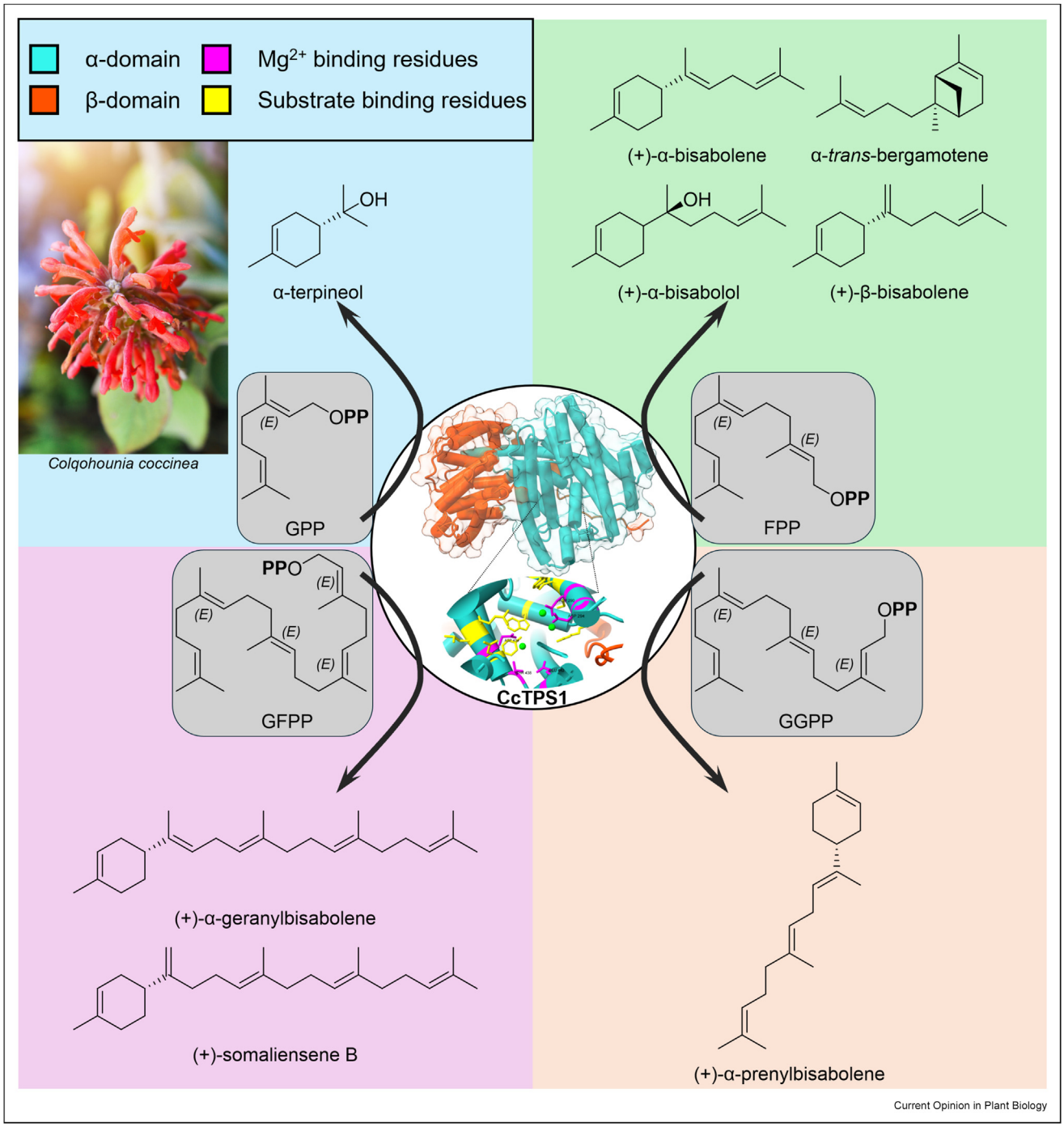


Protein architectures and phylogenetic tree of select plant terpene synthases from each subfamily.
Peptide sequences of representative TPSs were aligned by ClustalW, and a maximum likelihood tree was generated as in Figure 1 with branch lengths shown as the number of substitutions per site above and bootstrap values greater than 50% from 1000 iterations shown below branches. Each tip is labeled with the corresponding species and accession number, and branches are colored according to TPS subfamily membership (shown in the upper right corner). Structural models of representative proteins are displayed next to the corresponding sequences highlighted by red circles. TPSs are grouped and shaded based on their general activity class as shown on the right. A schematic of the corresponding peptide sequence alignment is shown on the left of the phylogenetic tree with solid vertical lines representing positional amino acid presence for each protein. The corresponding domain architectures are also shown for each protein (γ, yellow; β, dark orange; α, light blue). The black arrow (within Class I, II, II/I group) indicates the position of *Calohypnum plumiforme* isoprene synthase (CpKSL1/CpISPS) [GenBank: BEH00593.1]. Protein structures were obtained from published PDB structures (Q40622, 2ONG; Q38802, 3PYA) or EMBL-EBI AlphaFold predicted [121,122] structures (Q84UV0, AF-Q84UV0−F1; Q8SA63, AF-Q8SA63-F1; Q675L1, AF-Q675L1-F1; Q39548, AF-Q39548-F1; D8RLD3, AF-D8RLD3-F1) except for (A0A8U0DA95) which was modeled using ColabFold [123]. All structures were aligned to Q38802 (indicated by a red arrow) for which the protein crystal structure has been published (PDB: 3PYA), and the different domains were colored based on InterProScan [124] designations using UCSF ChimeraX [125].

also utilize olefinic substrates such as squalene for triterpenoid biosynthesis [47,48]. Members of class II frequently use GGPP as a substrate towards the production of phytohormones through *ent*-copalyl diphosphate (*ent*-CPP), but they are also involved in secondary metabolite production [18,27]. In lower plants [49,50] and gymnosperms [51], a subset of bifunctional class II/I TPSs possess both of the aforementioned activities and carry out sequential cyclization and dephosphorylation of GGPP that typically requires separate class II and class I TPSs in angiosperms [7,52].

Class I TPSs in plants can also be subdivided based on sequence similarity into canonical TPSs found across the plant kingdom and non-canonical microbial-terpene synthase-like (MTPSL) proteins which have been identified only in non-seed plants [53−55] (Figure 1). *MTPSL* genes in non-seed plants form four separate subclades, each of which encodes catalytically active TPSs, but with substantial primary sequence diversity even within the normally conserved aspartate-rich motif (DDxxD) where, for example, subclade III only contains the first DD of this motif [53]. Other groups of non-canonical TPSs have been identified outside of the plant kingdom including UbiA-related class I TPSs in fungi and bacteria [56−58], and bifunctional PT/class II TPSs [59] as well as class I triterpene synthases in fungi [60]. While UbiA-related proteins are found in plants, none of them, to the best of our knowledge, have been shown to display strict TPS activity; therefore, they will not be further considered here. Regardless of the TPS class and subfamily, in all cases, the enzyme structure is essential to maintaining its functional integrity as the carbocation intermediate(s) is highly reactive and could alkylate neighboring nucleophilic amino acids within the enzyme cavity or be vulnerable to water capture [18]. Consistent with these constraints, the active site for class I TPSs is buried within the characteristic α fold [61], while for class II TPSs, it is found between the β and γ domains [27,62] (Figure 2). Beyond the

Figure 3



Promiscuity of *Colquhounia coccinea* TPS1. *Colquhounia coccinea* terpene synthase 1 (CcTPS1; Genbank: QZL13763.1) is shown as an example of an 'extremely promiscuous enzyme' capable of catalyzing TPS reactions from multiple prenyl diphosphate substrates shaded in gray [77]. A structural model of CcTPS1 is presented in the middle with the compounds produced from different substrates surrounding it. The reaction center is located within the α-domain (light blue) containing predicted substrate-binding (yellow) and divalent metal cofactor-binding residues (magenta), that are typically required for terpene synthase activity. CcTPS1 was modeled in conjunction with three Mg^{2+} ions (light green) using AlphaFold3 [126]; domains and key residues were predicted using InterProScan [124], and the model was visualized with UCSF ChimeraX [125]. Photo credit for image of *Colqohounia coccinea*: ©cocorattanakorn/Adobe Stock.

conservation of this architecture, TPS primary sequences often share more similarity with other TPSs producing different products within a plant order than with those responsible for the same activity in another species, suggesting that primary sequence alone may be insufficient to predict the terpenoid product profile [63].

Members of multiple TPS subfamilies catalyze formation of the same product

Despite the occurrence of *TPS* genes in all major lineages of land plants, canonical *TPS* genes of class I, class II, and class II/I were found to be entirely absent from all analyzed green algae [64] which was further supported by a recent analysis of green algae transcriptomes (158) and genomes (31) [**32]. Across land plants, however, distinct subfamilies of TPSs from TPS-a to TPS-h have been characterized and they are separated based on phylogenetic similarities that can be seen in their overall protein structures and domain architectures (Table 1, Figure 1B and 2) [19]. However, only members of the TPS-c subfamily, which harbors class II *ent*-CPP synthases (CPSs) and class II/I dual activity CPS, and kaurene synthase (KS) (CPSKS), universally occur in land plants [**32,65]. Interestingly, while members of TPS-c are primarily implicated in phytohormone biosynthesis, this subfamily has been dramatically expanded in non-seed plants where the function of many of these proteins remains unknown [19,**32]. In the moss *Calohypnum plumiforme* (hypnum moss), a novel *ent*-kaurene synthase–like protein (CpKSL1/CpISPS) belonging to the aforementioned group that also clusters closely with members of TPS-e/f and TPS-h (Figure 1b and 2), was characterized as an isoprene (C_5) synthase even though it lacks sequence similarity to canonical isoprene synthases, which generally belong to the TPS-b subfamily [11,**66]. Moreover, CpKSL1 contains the characteristic DDxxD motif and α/β domains [**66] resembling the architecture of TPS-a, b, g, d1, and some TPS-e/f members, all of which, like CpKSL1, display class I TPS activity [19,67] (Table 1 & Figure 2). Despite only limited sequence similarity with other isoprene synthases and the lack of the four conserved residues in vascular plant isoprene synthases that predict the probability of isoprene synthase activity (i.e. isoprene score) [11], CpKSL1 has a similar active site structure to poplar isoprene synthase, implicating the involvement of other amino acids in catalysis [**66]. The occurrence of isoprene emission in mosses [68], which lack members of the TPS-b subfamily [**32], may emphasize the additional roles of TPS-c or MTPSLs beyond primary metabolism [**66]. Even within higher plants, isoprene-producing enzymes belonging to the TPS-b subfamily do not always group together with the monophyletic clade of isoprene synthases found in rosids and, like in hops, might have other biochemical functions [11,69]. The widespread occurrence and sequence divergence of isoprene synthases, across plant lineages and TPS subfamilies, further highlights the importance of isoprene production and likely supports the relevance of this compound in plant communication and stress response, while also highlighting the overlapping biochemical activities of phylogenetically unrelated TPSs [70,71].

TPS functional promiscuity: one enzyme, multiple products

Product promiscuity is frequent throughout TPSs [44,72–74]; however, most members of the angiosperm-specific TPS-b subfamily produce a single monoterpene product. In addition, single-product hemiterpene, sesquiterpene, and diterpene synthases (diTPSs) as well as promiscuous TPSs utilizing multiple prenyl diphosphate substrates belong to this subfamily. Some single-product diTPSs within the TPS-b subfamily include *Eremophila lucida* (shining poverty bush) ElTPS31 [75] and *Tripterygium wilfordii* (thunder god vine) TwTPS27 [76], which catalyze class I diTPS reactions to form (3*Z*,7*Z*,11*Z*)-cembratrien-15-ol from NNPP and an abietane-type diterpene, miltiradiene, from CPP, respectively. An example of an 'extremely promiscuous' member of the TPS-b subfamily is *Colquhounia coccinea* (Himalayan mint shrub) CcTPS1, which was found to accept GPP, FPP, GGPP, and GFPP to form a suite of corresponding terpenoids in vitro, although in planta, the monoterpene and sesterterpene products were not detected [77] (Figure 3). Therefore, subcellular localization of such promiscuous TPSs and availability of prenyl diphosphate substrates in the corresponding cellular compartment will determine the product profile which could vary based on plant species, tissue type, and developmental stage [10,78]. The promiscuity within the TPS-b subfamily is further illustrated in *Lathyrus odoratus* (sweet pea) where both LoTPS4 and LoTPS7 catalyze, respectively, the formation of 5 and 11 monoterpenes from GPP, as well 6 and 13 sesquiterpenes from FPP [79]. Surprisingly, they also catalyzed a similar series of reactions when *cisoid* substrates NPP and (*Z*,*Z*)-FPP were supplied [79]. Analogous TPS promiscuity within *L. odoratus* extends to LoTPS3 and LoTPS8, members of TPS-a, as well as LoTPS12, which belongs to the TPS-g subfamily. LoTPS3 uses both *cisoid* and *transoid* 10-carbon and 15-carbon prenyl diphosphates, while LoTPS8 prefers *cis* prenyl diphosphates, and LoTPS12 accommodates only all *trans* substrates. In addition, each TPS also exhibits product promiscuity yielding multiple terpene products from the accepted prenyl diphosphate substrates [79].

Product promiscuity is not surprising given the TPS mechanism often involves a reactive carbocation intermediate and non-specific charge migration within the active site that can be quenched at multiple positions [18,39,80]. Therefore, the resulting substrate and

product specificity is largely driven by stabilization of the carbocation intermediate by amino acids within the active site [*81] and is guided by coordinated amino acid pairs spanning the N-terminal and C-terminal domains [*82]. While the majority of studies surrounding product selectivity have focused on residue changes within the active site, recently it has been shown that, depending on the nature of TPSs, interdomain connectivities can also contribute to the product output and can be a more essential driving force than connectivities within the catalytic domain [*82]. In closely related TPSs, single-nucleotide polymorphisms (SNPs) can lead to amino acid changes favoring different end products [*81,83,*84,85]. These SNPs may have a dramatic influence on the terpenoid bouquet produced by a plant or specific tissue, not only by changing the product profile of a TPS through amino acid substitutions but also by altering the promoter region which affects the transcriptional regulation of the corresponding genes in response to various cues [83] or by promoting variable splicing variants to yield distinct TPS transcripts from a single gene [86].

In recent years, the importance of *TPS* promoter regions and regulation by transcription factors (TFs) has become more apparent. In addition, some plant genomes contain *TPS*s within biosynthetic gene clusters that allow coregulation of gene expression [87], highlighting the importance not only of *TPS* sequence and corresponding protein structure but also of the surrounding genome architecture for the encoding genes [88]. While epigenetic studies have demonstrated the effect of histone modifications in regulation of other specialized metabolic processes [89–92], such work in relation to terpene synthase expression is limited [93]. However, it is evident that alterations in the accessibility of genes to transcriptional machinery play a key role in the spatiotemporal expression of genes involved in terpenoid biosynthesis [88,94]. Beyond typical stress-responsive TFs, a growing list of those that directly regulate *TPS* expression and terpenoid biosynthesis have been characterized [93,95]. For example, in *Lilium* 'Siberia' (an Oriental hybrid lily), LiNAC100, a plant-specific 'no apical meristem (NAM), ATAF1,2, cup-shaped cotyledon (CUC2)' (NAC) TF, activates linalool synthase expression by directly binding its promoter region [96]. In *Lavandula angustifolia* (English lavender), another TF, LaMYC7, directly binds to the promoter region of caryophyllene synthase (*LaTPS76*) to induce its expression in glandular trichomes in response to methyl jasmonate [97]. Interestingly, LaMYC7 specifically interacted with the promoter region of only *LaTPS76*, even though the *L. angustifolia* genome also encodes another caryophyllene synthase, *LaTPS26*. Such specific control of *TPS* expression may present one mechanism of transcriptional regulation of multiple copies of closely related *TPS* genes [*73,98,99]. Retention of multiple *TPS* copies could be supported by positive selection, as seen in *Phoebe bournei* (a member of the Lauraceae), where defense against pathogens in aerial and root tissues likely resulted in multiple gene duplicates for members of *TPS-a* and *TPS-b* subfamilies totaling 34 and 28 members, respectively [*100]. Together, forming 13 clusters in the genome, members of *TPS-a* were preferentially expressed in the aerial tissue, whereas *TPS-b* members were expressed in roots [*100]. Furthermore, numerous duplication events of *TPS-a* subfamily members in the chicory genome, as well as of *TPS-a* and TPS-*b* subfamilies in *Wurfbainia villosa* (a member of the Zingiberaceae) and celery, enhanced terpene biosynthesis in these species [*73,101,102]. These duplications enabled fine-tuned *TPS* expression through differential modifications in promoter regions that interact with various sets of TFs under constantly shifting metabolic contexts [*73,101,102].

Conclusions and open questions

The ever-increasing understanding of TPSs is essential for metabolic engineering aimed at improving yields of high-value terpenoid products and provides fundamental knowledge into the biosynthesis of such a structurally and functionally diverse group of compounds. There is no doubt that the diversity of terpenoid products is, in part, driven by the great diversity of TPSs throughout the plant kingdom. Remarkably, for a long time, *trans*-prenyl diphosphates were the only known physiological substrates for short-chain TPSs, and over recent years, a substantial body of literature suggests that *cisoid* substrates are frequently occurring and accepted by numerous plant TPSs [10,16,75]. Further investigation into the mechanistic details favoring TPS activity with *trans*- versus *cis*-prenyl diphosphates will reveal the molecular constraints for driving such reactions. It is interesting that with the exceptional promiscuity of TPSs in vitro, many of the products are not found in planta. Such a result could be primarily due to the different localization of the enzymes and corresponding prenyl diphosphate substrates, which makes identification of TPS localization and the availability of substrates in the same compartment of paramount importance for determining the biological significance of in vitro findings. In addition, transcriptional and epigenetic regulation of *TPS* expression could further contribute to in planta product profiles; unfortunately our knowledge about these regulatory processes is still limited. The discrepancy between in planta and in vitro terpenoid profiles can also be the result of further modification of TPSs' products by endogenous enzymes, as exemplified in the metabolism of sesquiterpene volatiles in maize [103,104]. Finally, it is possible that recent *TPS* duplication and neofunctionalization, which have not yet been optimized in biochemical properties and expression profile, can contribute to the absence of their products in

planta. Even then, the product promiscuity of TPSs could be subject to positive selection as a mechanism to avoid resistance of pathogens and herbivores to a single initially potent compound and favor an endogenous combinatorial approach, while simultaneously maintaining highly specific TPSs for essential signaling and primary metabolic roles.

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.

Data availability

No data was used for the research described in the article.

Acknowledgements

For the sake of brevity, we have presented only select examples, however the absence of reference to the plethora of other excellent research regarding terpenoid biosynthesis is not intended to diminish their significance to the field. This work was supported by grants from the National Science Foundation IOS-2139804, the USDA National Institute of Food and Agriculture 2020-67013-30885, and by the USDA National Institute of Food and Agriculture Hatch Project number 177845 to ND.

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** of outstanding interest

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