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Harvesting the biosynthetic machineries that cultivate a variety of indispensable plant natural products

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Plants are a sustainable resource for valuable natural chemicals best illustrated by large-scale farming centered on specific products. Here, we review recent discoveries of plant metabolic pathways producing natural products with unconventional biomolecular structures. Prenylation of polyketides by aromatic prenyltransferases (aPTases) ties together two of the major groups of plant specialized chemicals, terpenoids and polyketides, providing a core modification leading to new bioactivities and downstream metabolic processing. Moreover, PTases that biosynthesize *Z*-terpenoid precursors for small molecules such as lycosantalene have recently been found in the tomato family. Gaps in our understanding of how economically important compounds such as cannabinoids are produced are being identified using next-generation 'omics' to rapidly advance biochemical breakthroughs at an unprecedented rate. For instance, olivetolic acid cyclase, a polyketide synthase (PKS) co-factor from *Cannabis sativa*, directs the proper cyclization of a polyketide intermediate. Elucidations of spatial and temporal arrangements of biosynthetic enzymes into metabolons, such as those used to control the efficient production of natural polymers such as rubber and defensive small molecules such as linamarin and lotaustralin, provide blueprints for engineering streamlined production of plant products.

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Introduction

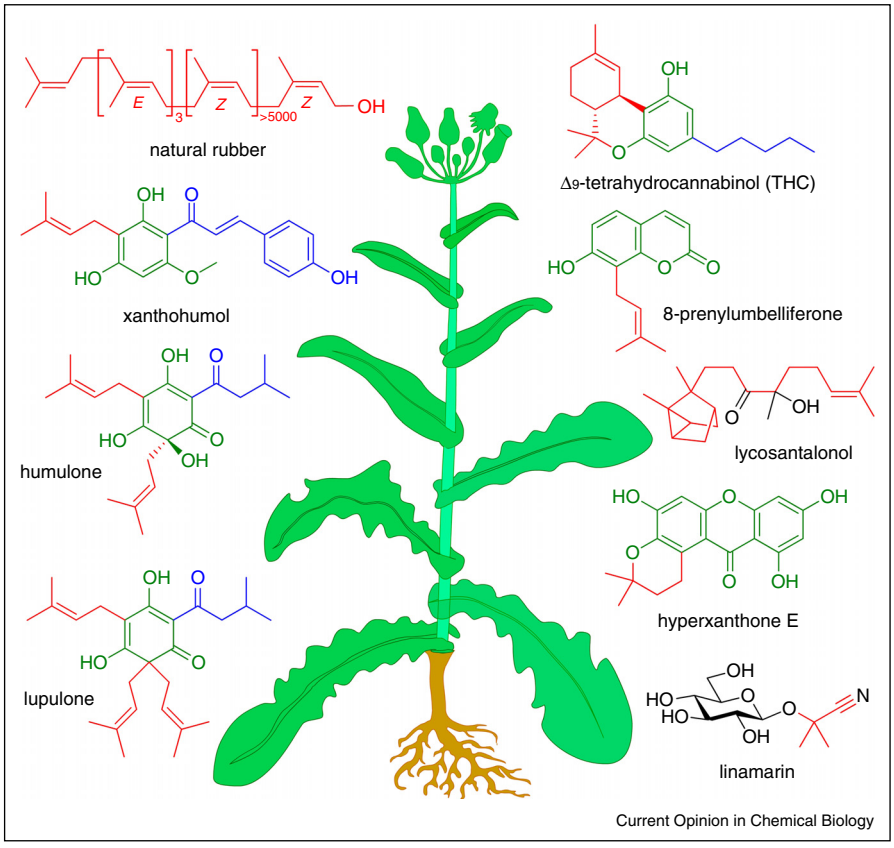
Plants are a rich source of commercially relevant natural products commonly used as agricultural chemicals, nutraceuticals, therapeutics, flavors, and fragrances [1,2]. In particular, terpenes and terpenoids, polyketides and associated phenylpropanoids, and alkaloids (reviewed by O'Connor *et al.* in this issue) are commonly associated with plant metabolism [3,4]. As analytical methods improve with increasing sensitivities and lower costs, examinations of well-studied plant models, as well as new plant specimens, continue to reveal unexpected chemical structures. Often these molecules contain building blocks derived from two or more distinct classes of plant-specialized metabolites. The isolation and structure elucidation of such compounds portend yet to be discovered enzymes, mechanisms, and assemblies of biosynthetic pathways [5].

As biotic and abiotic factors fluctuate appreciably across a myriad of plant ecological niches, these specialized metabolic pathways provide host populations with enhanced fitness while exhibiting both spatial and temporal control across specific tissues and cells (Figure 1). An increasing appreciation of plant natural product biosynthesis, driven by high-content and cost effective metabolomic, transcriptomic, and genomic surveys integrated with ecology, biochemistry and heterologous expression, has expanded our understanding of mechanistic and organizational strategies that have evolved across the green plant lineage to produce structurally complex and specialized bioactive metabolites. This review highlights recent advances in plant biochemistry that utilize multidimensional approaches and disciplines to uncover and manipulate these newly discovered biosynthetic pathways.

Natural products arising from aromatic prenyltransferases (aPTases)

Aromatic polyketides formed by type III polyketide synthases (T3PKSs) and terpenes/terpenoids formed by terpene synthases (TPSs) are well-known and abundant classes of plant natural products with a wide variety of uses by humans and functions *in planta* [6]. These two classes of compounds have been extensively studied with respect to their structural diversity, economic value, pharmacological properties, and biosynthetic origins [7••,8]. Recently, plant molecules that contain multiple molecular motifs originating from disparate biosynthetic pathways are garnering widespread interest for their novelty and commercial value [9–11]. Prenylated aromatic polyketides are prevalent throughout the plant lineage, suggesting an important biosynthetic and evolutionary role for the aPTases responsible for their production

Figure 1



Specialized metabolites from plants. Segments of the molecules depicted are color-coded based on biosynthetic origin. Molecules in green are derived from T3PKSs, red derived from PTases, blue derived from fatty acid or amino acid anabolic and catabolic pathways, and black derived from an assortment of other biosynthetic pathways. *E or Z* configurations are shown for natural rubber to highlight the absolute stereochemistry of its double bonds.

(Figures 1 and 2a). While aPTases from other organisms, such as bacteria and fungi, are often cytosolic and soluble, plant aPTases tend to be integral membrane proteins [12,13]. The installed prenyl moieties are essential for tuning and expanding the bioactivity and downstream metabolic processing of aromatic products, as demonstrated for the plant terpene-flavonoid polyketide 8-prenylnaringenin (Figure 2a) [14–16].

Investigation of *Hypericum calycinum* (Great St. John's Wort), a source of pharmacologically active specialized metabolites, led to the identification of a membrane-bound aPTase that elaborates xanthone polyketides [17]. This aPTase transfers a 5-carbon dimethylallyl moiety onto 1,2,6,7-tetrahydroxyxanthone to redirect polyketide biosynthesis to tailored natural products such as hyperxanthone E (Figure 1), a compound exhibiting anti-inflammatory properties [18].

In *Petroselinum crispum* (parsley), an aPTase named PcPT was discovered that is specific for the modification of coumarin derivatives [19•]. PcPT adds a dimethylallyl moiety to umbelliferone, the product of which serves as the substrate for downstream enzymes that together generate bioactive furanocoumarin molecules such as angelicin [20]. Like many specialized metabolic enzymes of plants that exhibit relaxed regiospecificity (Figure 2a), the dimethylallyl group can be added at either of two positions to produce a 6-prenyl or 8-prenyl product. While many aPTases will prenylate a variety of substrates [21,22], PcPT, while displaying relaxed regiospecificity, maintains high selectivity for umbelliferone.

A phylogenetically similar aPTase was discovered in *Citrus limon* (lemon), dubbed ClPT [23••]. In contrast to PcPT, ClPT transfers a 10-carbon geranyl unit onto the C-8 of umbelliferone. While many aPTases will accept a variety of substrates, ClPT is very specific towards coumarin molecules. CIPT does not exhibit transferase activity with furanocoumarins, coumaric acid derivatives, flavonols or isoflavones.