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REVIEW

Phenolic sucrose esters: evolution, regulation, biosynthesis, and biological functions

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Abstract

Phenolic sucrose esters (PSEs) are a diverse group of specialized metabolites that are present in several angiosperm lineages. Phylogenetic reconstruction and structural variation suggest that these metabolites may have evolved independently in monocots and dicots. Constitutive variation in PSE abundance across plant organs and developmental stages is correlated with transcriptional regulation of the upstream phenylpropanoid pathway, whereas pathogen induction is regulated by stress-related phytohormones such as ethylene. Shared structural features of PSEs indicate that their biosynthesis may involve one or more hydroxycinnamoyl transferases and BAHD acetyltransferases, which could be identified by correlative analyses of multi-omics datasets. Elucidation of the core biosynthetic pathway of PSEs will be essential for more detailed studies of the biological function of these compounds and their potential medicinal and agricultural applications.

Keywords Phenolic sucrose esters · Plant defense · Plant specialized metabolism

Introduction

Phenolic acids, one of the most structurally diverse groups of plant specialized metabolites, are not only essential components of plant responses to various environmental stresses, but also have potential human health benefits. Aromatic amino acids are precursors for the biosynthesis of phenolic acids, including benzoic acid, cinnamic acid, and their hydroxylated and methoxylated derivatives. The structural diversity of these simple phenolic acids is further expanded by esterification of the carboxyl group with assorted hydroxyl-containing molecules. Chlorogenic acids, for example, are caffeoylquinic acid esters involved in plant responses to microbial infection and oxidative stress (Clifford et al. 2017). Due to their antioxidant activities and other potential human health benefits, these compounds are also sold commercially. More recently, additional phenolic esters, in particular phenolic sucrose esters (PSEs; Fig. 1) with promising biological activities, have been discovered.

PSEs are formed by esterification of the carboxyl group of one or more phenolic acids with free hydroxyl groups on a sucrose molecule. Most plant PSEs are also acetylated on one or more hydroxyl groups of the sucrose. Hence, the position and number of phenolic and acetyl moieties are the main drivers of PSE diversity (Fig. 1). Although the phenolic moieties enable detection of PSEs by ultraviolet absorbance, specific identification of these compounds relies on liquid chromatography-mass spectrometry. The ester bonds of PSEs are easily broken, even under moderate collision energy (20–40 V), such that the dominant daughter ions are usually related to the more ionizable phenolic moieties (Zhou et al. 2019b).

PSEs were first identified in *Raphanus sativus*, and later in wide variety of plant species that are commonly used as alternative medicine ingredients (Table 1). Crude plant

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Fig. 1 Natural sources and structural diversity of phenolic sucrose esters. Examples of plants rich in PSEs including *Raphanus sativus* (top left; Stoughton 2008), *Polygala tenuifolia* (top right; Yazbek 2006), *Zea mays* (bottom left; Voekler 2010), and *Polygonum cuspidatum* (bottom right; Rice 2009), and their characteristic PSE compounds. Natural PSEs vary in the number and position of phenolic acid moieties and acetylation on the sucrose backbone

extracts that are rich in these compounds, and in some cases purified compounds, have demonstrated anti-oxidative and cytotoxic activities in vitro (Panda et al. 2011). These promising bioactivities have sparked interest in the development of organic synthesis methods to produce both natural PSEs and their structural analogs (Panda et al. 2012a, b).

In contrast to recent advances in understanding the medical applications and chemical synthesis of PSEs, their ecological functions and biosynthetic pathways remain largely unknown, and the published results are mostly correlative. This lack of progress is at least partly to the absence of genomic resources and molecular biology techniques for investigating the non-model medicinal plants in which PSEs historically have been identified and studied. Recent non-targeted metabolomics assays of rice (*Oryza sativa*) and maize (*Zea mays*) have led to the identification of several PSEs in these staple crop species (Chen et al. 2014; Zhou et al. 2019b). The rich resources and technological platforms that are available for rice and maize will facilitate further investigation of PSE biosynthesis and regulation. There is increasing experimental evidence that associates PSEs with plant defense against biotic stresses, suggesting novel translational applications that enhance stress resistance of crops by targeted engineering of PSE production in plants or development of PSE-based biopesticides (Balmer et al. 2013; Dowd et al. 2018; Zhou et al. 2019b).

In this review, we summarize the identification of structurally diverse PSEs across angiosperms, develop a phylogenetic framework to infer the evolution of this class of specialized metabolites, propose potential genetic regulation and a biosynthetic pathway of PSEs, and discuss current experimental evidence supporting applications of PSEs in agriculture.

Structural diversity of phenolic sucrose esters demonstrates phylogenetic disparity between monocots and eudicots

Since their initial discovery in *Raphanus sativus* in 1980, 202 structurally distinct PSEs have been identified in 26 angiosperm families of belonging to 16 distinct orders (Table 1; Supplemental Table 1, 2). The wide taxonomic distribution of PSEs is perhaps not surprising, given that both sucrose and phenolic acids are almost ubiquitously present in angiosperms. The Liliales contain 13 PSE-producing species belonging to the Smilaceae and Liliaceae families. Interestingly, two large eudicot orders, the Fabales and Caryophyllales, contain more known PSE-producing species than the Liliales, underlining the prevalence of these metabolites across angiosperm lineages. Although the current summary represents the known taxonomic distribution

Table 1 Literature summary of reported natural PSEs

Species	Family	Order	Number of PSEs	Named PSEs	References
Calamus quiquesetinervius	Arecaceae	Arecales	5		(Chang et al. 2010)
Bidens parviflora	Asteraceae	Asterales	2		(Wang et al. 2003)
Lindelofia stylosa	Boraginaceae	Boraginales	3		(Choudhary et al. 2006)
Lindelofia stylosa	Boraginaceae	Boraginales	4		(Begum 2007)
Iberis amara	Brassicaceae	Brassicales	1		(Fabre et al. 2000)
Raphanus sativus	Brassicaceae	Brassicales	1		(Linscheid et al. 1980)
Raphanus sativus	Brassicaceae	Brassicales	7	Raphasativuside A-B	(Kim et al. 2015)
Beta vulgaris	Amaranthaceae	Caryophyllales	1	Arillatose B	(Bokern et al. 1991)
Froelichia floridana	Amaranthaceae	Caryophyllales	1		(Wang et al. 2009)
Vaccaria segetalis	Caryophyllaceae	Caryophyllales	1	Segetoside A	(Sang et al. 1998)
Bistorta manshuriensis	Polygonaceae	Caryophyllales	5	Bistoroside A-B, Helonioside A-B, Smilaside L	(Kim et al. 2010)
Fagopyrum dibotrys	Polygonaceae	Caryophyllales	2		(Wang et al. 2005)
Fagopyrum tataricum	Polygonaceae	Caryophyllales	8	Diboside A, Tatarisides A-G	(Zheng et al. 2012)
Persicaria orientalis	Polygonaceae	Caryophyllales	2		(Masum et al. 2019)
Polygonum cuspidatum	Polygonaceae	Caryophyllales	5	Hydropoperoside, Lapathoside A, C, Vanicoside A-B	(Fan et al. 2009)
Polygonum hydropiper	Polygonaceae	Caryophyllales	1	Hydropiperoside	(Fukuyama et al. 1983)
Polygonum hydropiper	Polygonaceae	Caryophyllales	5		(Kiem et al. 2008)
Polygonum lapathifolium	Polygonaceae	Caryophyllales	2	Lapathoside A, Vanicoside B	(Takasaki et al. 2001a)
Polygonum lapathifolium	Polygonaceae	Caryophyllales	6		(Takasaki et al. 2001b)
Polygonum pensylvanicum	Polygonaceae	Caryophyllales	3		(Zimmermann and Sneden 1994)
Polygonum pensylvanicum	Polygonaceae	Caryophyllales	10		(Brown et al. 1998)
Polygonum perfoliatum	Polygonaceae	Caryophyllales	7		(Sun et al. 2000)
Polygonum perfoliatum	Polygonaceae	Caryophyllales	7	Helonioside A-B, Hydropiperoside, Lapathoside D, Vanicoside B, C, F	(Li et al. 2009)
Polygonum sachalinense	Polygonaceae	Caryophyllales	2		(Kawai et al. 2006)
Polygonum sachalinense	Polygonaceae	Caryophyllales	4	Hydropiperoside, Lapathoside C-D, Vanicoside B	(Fan et al. 2010)
Rumex dentatus	Polygonaceae	Caryophyllales	1	Helonioside A	(Zhu et al. 2006)
Triplaris americana	Polygonaceae	Caryophyllales	1	Vanicoside D	(Oliveira et al. 2008)
Bhesa paniculata	Celastraceae	Celastrales	5		(Harrison et al. 1995)
Monnina obtusifolia	Polygalaceae	Fabales	2		(Lepore et al. 2011)
Polygala aureocauda	Polygalaceae	Fabales	3		(Quang et al. 2019)
Polygala chamaebuxus	Polygalaceae	Fabales	6		(Hamburger and Hostettmann 1985)
Polygala glomerata	Polygalaceae	Fabales	8	Glomeratose A-D	(Zhang et al. 1998)
Polygala hongkongensis	Polygalaceae	Fabales	3		(Wu et al. 2007)
Polygala japonica	Polygalaceae	Fabales	6		(Quang et al. 2018)
Polygala reinii	Polygalaceae	Fabales	8		(Saitoh et al. 1994)
Polygala sibirica	Polygalaceae	Fabales	10		(Miyase et al. 1999)
Polygala tenuifolia	Polygalaceae	Fabales	6	Tenuifoliside A-C	(Ikeya et al. 1991)
Polygala tenuifolia	Polygalaceae	Fabales	2		(Ikeya et al. 1994)
Polygala tenuifolia	Polygalaceae	Fabales	5	Sibricose A1, A5, A6, Tenuifoliside A	(Tu et al. 2008)
Polygala tenuifolia	Polygalaceae	Fabales	1		(Hu et al. 2011)
Polygala tenuifolia	Polygalaceae	Fabales	3	Sibricose A5, A6	(She et al. 2011)
Polygala tricornis	Polygalaceae	Fabales	10		(Li et al. 2005)
Polygala virgata	Polygalaceae	Fabales	3		(Bashir et al. 1993)

Table 1 (continued)

Species	Family	Order	Number of PSEs	Named PSEs	References
Polygala wattersii	Polygalaceae	Fabales	5		(Kobayashi et al. 2000a)
Polygala wattersii	Polygalaceae	Fabales	5		(Kobayashi et al. 2000b)
Radix polygalae	Polygalaceae	Fabales	2		(Liu et al. 2010)
Securidaca longipedunculata	Polygalaceae	Fabales	2		(Tommasi et al. 1993)
Cynanchum amplexicaule	Apocynaceae	Gentianales	2		(Chen et al. 2008)
Cynanchum hancockianum	Apocynaceae	Gentianales	2		(Lou et al. 1993)
Kigelia pinnata	Bignoniaceae	Lamiales	2		(Yaser et al. 2006)
Salvia officinalis	Lamiaceae	Lamiales	1		(Wang et al. 1999)
Globularia orientalis	Plantaginaceae	Lamiales	2		(Caliş et al. 2002)
Snow Hebes	Plantaginaceae	Lamiales	1		(Taskova et al. 2010)
Crophularia ningpoensis	Scrophulariaceae	Lamiales	3	Acretoside, Arillatose B, Sibirioside A	(Hua et al. 2014)
Belamcanda chinensis	Iridaceae	Liliales	1	Shegansu C	(Lin et al. 1998)
Belamcanda chinensis	Iridaceae	Liliales	1		(Ha et al. 2019)
Heloniopsis orientalis	Liliaceae	Liliales	6	Helonioside A-D	(Nakano et al. 1986)
Heterosmilax erythrantha	Liliaceae	Liliales	3		(Nhiem et al. 2009)
Lilium henryi	Liliaceae	Liliales	4		(Shimomura et al. 1988)
Lilium longiflorum	Liliaceae	Liliales	3		(Shoyama et al. 1987)
Lilium mackliniae	Liliaceae	Liliales	9		(Sashida et al. 1991)
Lilium speciosum	Liliaceae	Liliales	9		(Shimomura et al. 1986)
Smilax bracteata	Liliaceae	Liliales	3		(Li et al. 2002)
Smilax bracteata	Liliaceae	Liliales	11	Helonisde A-B, Smilaside E-L	(Zhang et al. 2008)
Smilax china	Liliaceae	Liliales	9	Helonioside B, Smilaside A-F, Smiglaside E	(Kuo et al. 2005)
Smilax glabra	Liliaceae	Liliales	8	Helonioside A, Smiglaside A-E	(Chen et al. 2000)
Smilax riparia	Liliaceae	Liliales	4	Smilaside M-N	(Sun et al. 2012)
Trillium kamtschaticum	Liliaceae	Liliales	3		(Ono et al. 2007)
Paris polyphylla	Melanthiaceae	Liliales	1		(Wang et al. 2007)
Paris polyphylla	Melanthiaceae	Liliales	1		(Yan et al. 2008)
Phyllanthus niruri	Phyllanthaceae	Malpighiales	1	Niruriside	(Cutrone et al. 1996)
Aristolochia cretica	Aristolochiaceae	Piperales	2	Acretoside, Arillatose B	(Georgopoulou et al. 2005)
Cyperus rotundus	Cyperaceae	Poales	2		(Ryu et al. 2015)
Cyperus rotundus	Cyperaceae	Poales	2		(Sim et al. 2016)
Oryza sativa	Poaceae	Poales	6	Smilaside A	(Cho et al. 2015)
Zea mays	Poaceae	Poales	2	Smilaside A, Smiglaside C	(Zhou et al. 2019b)
Sparganium stoloniferum	Typhaceae	Poales	3		(Shirota et al. 1996)
Sparganium stoloniferum	Typhaceae	Poales	2		(Shirota et al. 1997)
Sparganium stoloniferum	Typhaceae	Poales	3		(Xiong et al. 2008)
Sparganium stoloniferum	Typhaceae	Poales	1		(Xiong et al. 2009)
Sparganium stoloniferum	Typhaceae	Poales	6		(Zong et al. 2018)
Prunus jamasakura	Rosaceae	Rosales	12		(Shimazaki et al. 1991)
Prunus mume	Rosaceae	Rosales	10	Mumeoses A-J	(Fujimoto et al. 2013)
Prunus mume	Rosaceae	Rosales	10	Mumeoses A-E, K-O	(Seikou et al. 2013)
Prunus mume	Rosaceae	Rosales	9	Mumeoses C-D, P-V	(Fujimoto et al. 2014)
Prunus padus	Rosaceae	Rosales	6		(Yoshinari et al. 1990)
Prunus ssiori	Rosaceae	Rosales	1		(Abdallah et al. 1994)
Prunus tomentosa	Rosaceae	Rosales	7	Tomensides A-D	(Zhao et al. 2014)
Ruta corsica	Rutaceae	Sapindales	1		(Cédric et al. 2004)
Ruta graveolens	Rutaceae	Sapindales	2		(Chen et al. 2001)

Table 1 (continued)

Species	Family	Order	Number of PSEs	Named PSEs	References
Canna edulis	Cannaceae	Zingiberales	2		(Yun et al. 2004)
Musa acuminata	Musaceae	Zingiberales	19		(Sandjo et al. 2019)

of PSEs, this list is almost certainly incomplete. In particular, since researchers are more likely to search for PSEs in taxonomic relatives of known PSE-producing species and negative results are often not reported in the literature, we expect that there is a strong sampling bias. Despite these caveats, integrating the current taxonomic distribution of PSE-producing species within a phylogenetic framework can still provide valuable insight into the putative evolutionary history of PSEs, thereby helping to elucidate the biosynthesis and genetic regulation of this class of specialized metabolites.

In an attempt to re-construct the evolution of PSEs in angiosperms, we mapped the PSE taxonomic distribution data summarized above to a recently updated angiosperm phylogeny (Yang et al. 2020). According to the existing literature, none of the basal angiosperm lineages include PSE-producing species. Similarly, no PSE-producing species are found in the more basal monocot orders, indicating that PSE production is not deeply conserved across all angiosperms. With the exception of the Asparagales, all of the more derived monocot orders contain at least one PSE-producing species, suggesting that PSE production may be a conserved trait that was present in the common ancestor of the Poales, Zingiberales, Arecales, Asparagales, and Liliales about 120 million years ago. However, since there has been only a single report of a PSE-producing arecaceous species (*Calamus quiquesetinervius*), it is still possible that PSE production has evolved independently within each monocot order (Chang et al. 2010). Among eudicots, PSE-producing species are scattered among both rosids and asterids, supporting multiple independent evolutionary origins in each lineage. While PSEs are mostly absent among basal eudicots and magnoliids, a single report in *Aristolochia cretica* suggests that these compounds either evolved independently in this species, or that there are as yet undiscovered PSE-producing species among the magnoliids (Georgopoulou et al. 2005) (Fig. 2).

Although PSEs are widely found across angiosperms, monocots and dicots (eudicots and magnoliids) tend to produce structurally distinct metabolites. Out of the 202 natural PSEs that have been reported, 27 were found in both monocots and dicots, 111 were reported only in eudicot and magnoliid species, and 62 were monocot-specific (Fig. 3a). To further parse the structural differences between monocot and dicot PSEs, we summarized the total number and type of esterification identified on these molecules by each of the eight free hydroxyl groups on the sucrose backbone (Fig. 3b). Both monocot- and dicot-produced PSEs tend to have three or less class-defining phenyl groups, while more than a dozen of tetra-phenolated PSEs have been identified in dicot species only (Fig. 3c). Interestingly, over half of the dicot-specific PSEs (57 out of 111) have no acetylation, whereas more than 75% of the monocot-specific PSEs (47 out of 62) contain at least one acetyl group (Fig. 3d). Each of the eight free hydroxyl groups also demonstrates distinct preference for the type of esterification (Fig. 3e). The 3′ position on the fructofuranose ring of the sucrose molecule is the primary site of phenolic esterification, with over 88% of the reported PSEs (178 out of 202) having a phenolic acid group attached here. Less preferred positions for phenolic acid attachment include the C6′ and C1′ hydroxyl groups on the fructofuranose ring (44% and 20%, respectively), and the C6 position on the glucopyranose ring (37%). Other than these four positions, phenolic acid groups are rarely found esterified to any of the remaining four free hydroxyl groups, suggesting that either these positions are chemically unsuitable for the attachment of the electron-dense phenolic acids, or accumulation of such PSEs imposes a fitness penalty on plants. The preference for phenolic acid esterification positions is similar between monocots and dicots, with two notable exceptions. Phenolic acid esterification of the C6 hydroxyl group on the glucopyranose ring is more prevalent among eudicots, whereas a larger proportion of monocot-derived PSEs contain a phenolic acid group attached to the C6′ position of the fructofuranose ring. Since the same hydroxyl group cannot be simultaneously esterified by a phenolic group and an acetyl group, it is not surprising that preferred phenolic acid attaching positions tend to be non-acetylated. Indeed, most acetylation is found on the glucopyranose ring of the sucrose backbone, to which phenolic groups are rarely attached. Interestingly, the C6 position of the glucopyranose ring and the C1′ position of the fructofuranose ring can have either phenolic acid groups or acetyl groups attached at comparable proportions in different PSEs (Fig. 3e). In addition to the previously mentioned difference in the overall extent of acetylation between monocot- and dicot-produced PSEs, these two groups of compounds also demonstrate a distinct positional preference for acetylation. For example, 33 out of 62 (53%) of PSEs found exclusively in monocots are acetylated at C6 position, whereas less

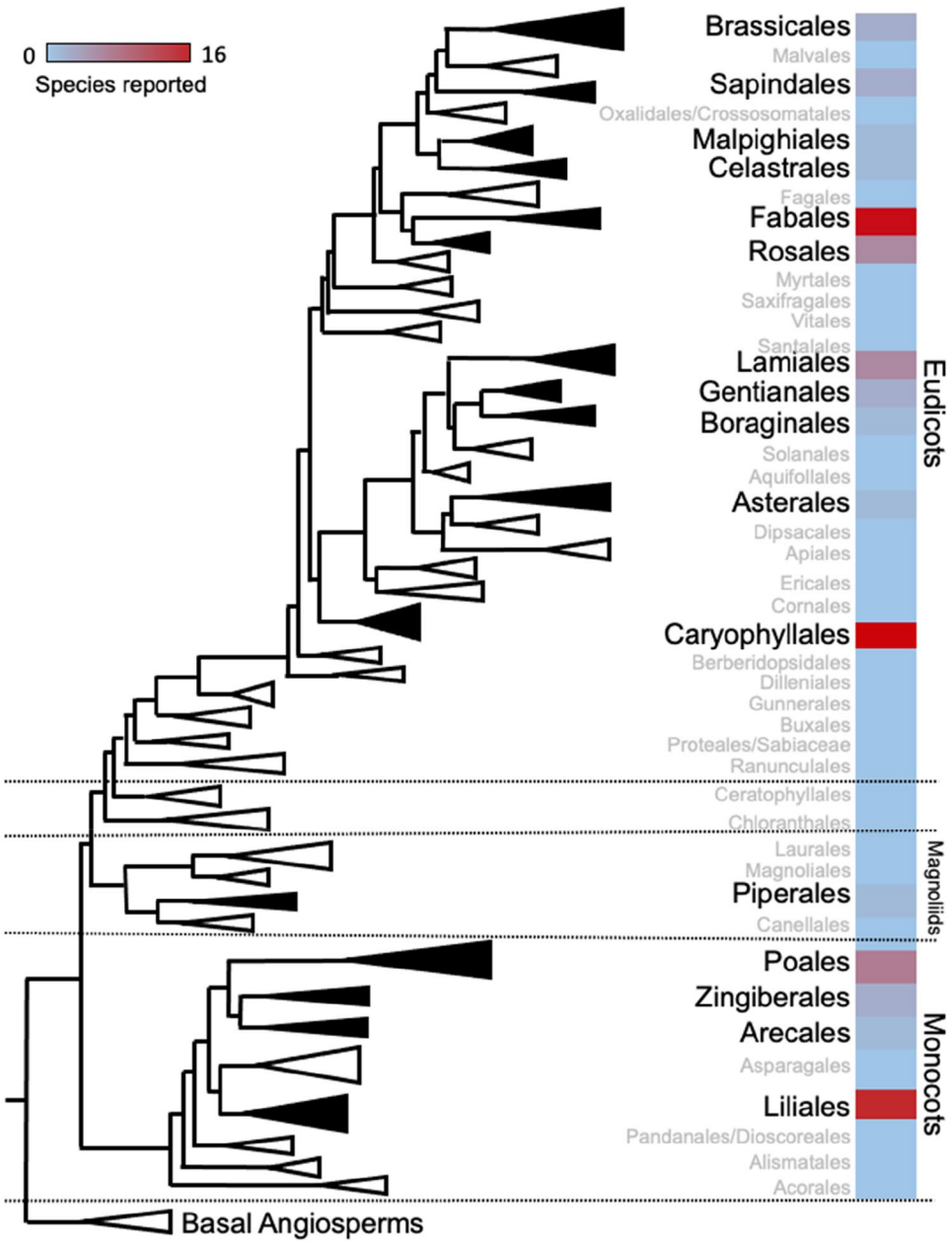

Fig. 2 Distribution of phenolic sucrose esters across the angiosperm phylogeny. PSE distribution in each angiosperm order is based on the literature survey summarized in Table 1. Orders in which PSEs have been reported are represented by black filled triangles on the phylogenetic tree and black text. Those without PSE are shown as blank triangles with grey text labels. The reported number of PSE-producing species in each order is shown on a blue-red color scale to the right of the order names

than 30% of dicot-specific PSEs (33 out of 111) have the same modification. By contrast, a higher proportion of PSEs only found in dicot species tend to be acetylated at the C1′, C3, and C4 positions compared to their monocot-specific analogs.

In summary, due to the scattered taxonomic distribution and likely incomplete investigation of PSEs in different plant species, there is insufficient information to reconstruct a detailed evolutionary history of this class of specialized metabolites. Nevertheless, as there are no reports of PSEs in basal monocots and eudicots, there are likely to be at least two independent origins of PSE biosynthesis in plants. This scenario is further supported by the limited overlap in specific PSEs between monocots and eudicots, positional preferences for the attachment of phenolic acid groups, and differences in their acetylation pattern.

Dynamic level of phenolic sucrose esters *in planta* shed light on the regulatory mechanism of these specialized metabolites

Similar to many other specialized metabolites, accumulation of PSEs also demonstrates clear organ and developmental stage specificity. Though early studies of PSEs rarely compared the abundance of these compounds in different plant

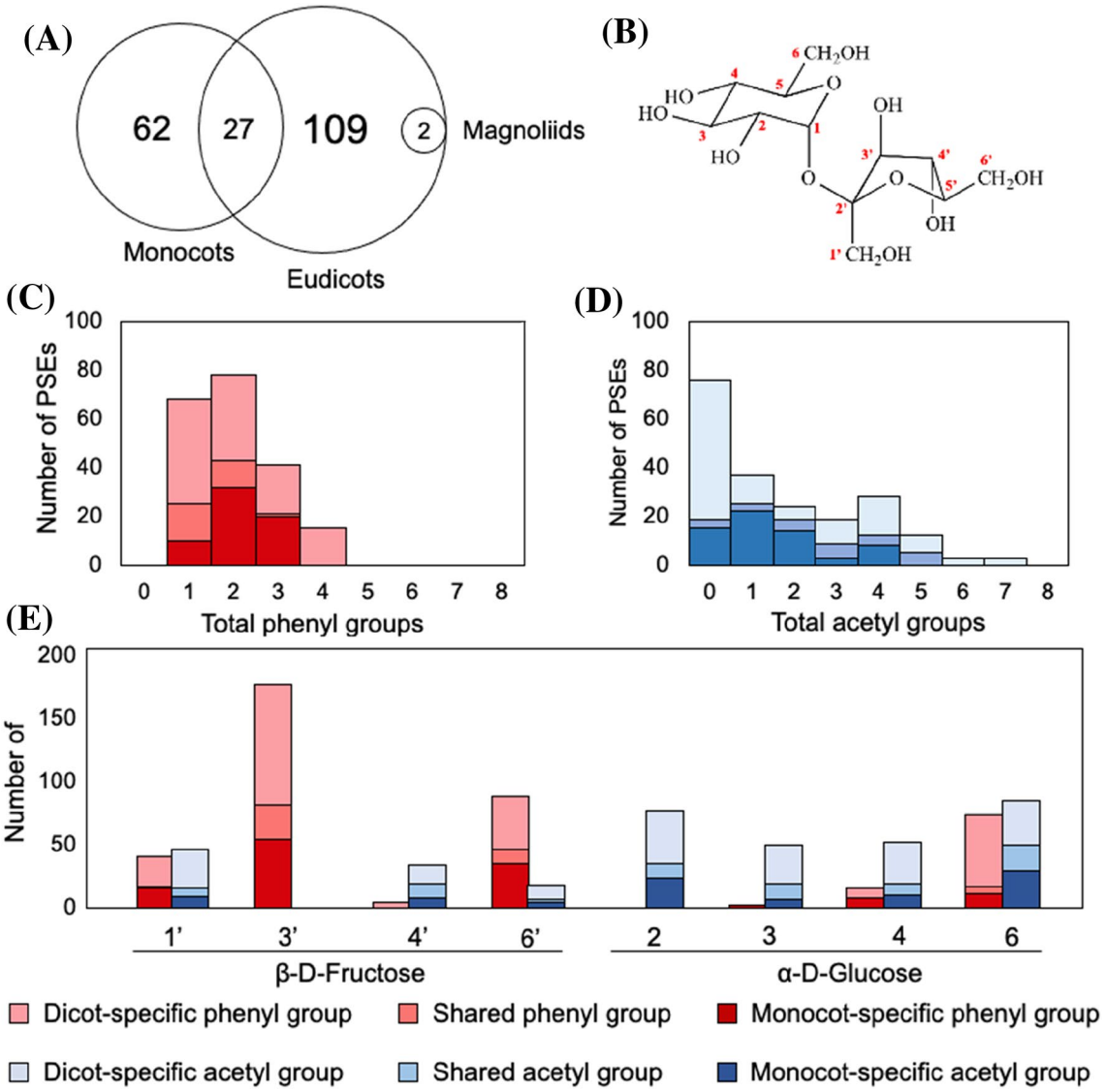

Fig. 3 Phenolic sucrose esters reported in monocots and dicots demonstrate distinct side chain structure modification patterns. Venn diagram of PSEs reported in monocots, eudicots, and magnoliids (**a**). Eight free hydroxyl groups are available for esterification with a side chain on a sucrose molecule (**b**). Distributions of the numbers of phenyl and acetyl esterification on the sucrose backbone are plotted for all reported PSEs (**c**, **d**). These modifications are separately summarized based on the type of modification and the class of plant where the modification is reported (**e**). The color codes for plant groups are shared across panels **c**–**e**

organs, indirect evidence of organ-specific distribution of PSEs can be traced to the deliberate selection of underground rhizomes (e.g. *Polygala tenuifolia, Smilax glabra*) and tubers (e.g. *Sparganium stoloniferum*) for use in traditional medicine. More recent non-targeted metabolomics analyses of crop species have provided more direct experimental evidence for the organ-specific accumulation of PSEs. The concentration of smilaside A (3,6-diferuloyl-3′6′-diacetylsucrose) was almost 30-fold higher in maize seedling roots compared to leaf tissues in the same batch of samples (Balmer et al. 2013). Consistent with this observation, a later comparative metabolomics study identified smilaside A, as well as its further acetylated derivative smiglaside C (3,6-diferuloyl-2′3′6′-triacetylsucrose), in maize roots but detected no PSE in leaf tissue from the same plants (Zhou et al. 2019b). Since both of these experiments involved 2–3 weeks old maize seedlings, the low-versus-none difference in PSE content in leaf tissues may be due to different detection thresholds of the mass spectrometry platforms and subsequent data processing pipelines. Examination of the newly emerged third leaves of over 250 maize genotypes, using the same non-targeted metabolomics platform as Zhou et al (2019b), did not show PSEs in any of the samples, suggesting that the absence of PSEs in young leaf tissue is a

widely conserved phenotype across the genetically diverse maize germplasm (Zhou et al. 2019a). In a separate experiment with 35-day-old maize plants, smilaside A and smiglaside C were detected in stem tissues (Zhou et al. 2019b). Smiglaside C also was detected in leaf tissue of rice plants at the five-leaf stage (Chen et al. 2014). These observations suggest that the organ-specific distribution of PSEs is also linked to the developmental stages of the organs.

A comparison of reportedly PSE-rich (rhizomes, tubers, roots, mature stems and leaves) and PSE-poor (seedling leaves) organs in maize and other medicinal plant species suggests that PSE content may be correlated with the level of tissue lignification. Since both lignin monomers and the phenolic moieties of PSEs originate from the general phenylpropanoid pathway, we hypothesize that the tissue- and developmental stage-specific accumulation of PSEs may result from transcriptional regulation of phenylpropanoid biosynthetic genes encoding phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate:CoA ligase (4CL). To test this hypothesis, we collected published transcriptomics datasets from seedling roots and leaves of maize (*Zea mays*) and rice (*Oryza sativa*) from qTeller (qteller.maizegdb.org) and IC4R Expression Database (expression.ic4r.org) respectively for comparison between tissue types (Supplemental Table 3). In support of our hypothesis, expression levels of phenylpropanoid biosynthetic genes in both maize and rice were consistently higher in seedling roots than shoots, suggesting that the organ-specific distribution of PSEs may indeed be a result of transcriptional regulation of the phenylpropanoid pathway that likely supplies the phenolic moieties for PSE biosynthesis (Fig. 4). Interestingly, a recent study involving a maize *CINNAMYL ALCOHOL DEHYDROGENASE 2*-deficient mutant (*zmcad2*) found significantly elevated levels of various phenyl hexoses, including one compound with an almost identical exact mass as smiglaside C (Liu et al. 2020). This observation further supports our hypothesis that the PSE biosynthetic pathway represents an independent competing branch of the lignin monomer biosynthesis, downstream of the core phenylpropanoid pathway.

In addition to constitutive variation across organs and developmental stages, studies on maize have shown that PSE accumulation is inducible by diverse phytopathogenic fungi. In both leaves and roots of maize seedlings, *Colletotrichum graminicola* infection induced significant accumulation of smilaside A (Balmer et al. 2013). Although the absolute level of smilaside A was an order of magnitude lower in leaves than roots, irrespective of the infection status, the inducibility was higher in leaves, as measured by the fold-change of this compound after infection. Similarly, smilaside A and/or smiglaside C were significantly induced in maize plants inoculated with *Aspergillus flavus, Rhizopus microspores, Fusarium graminearum, F. verticillioides*, and *Cochliobolus*

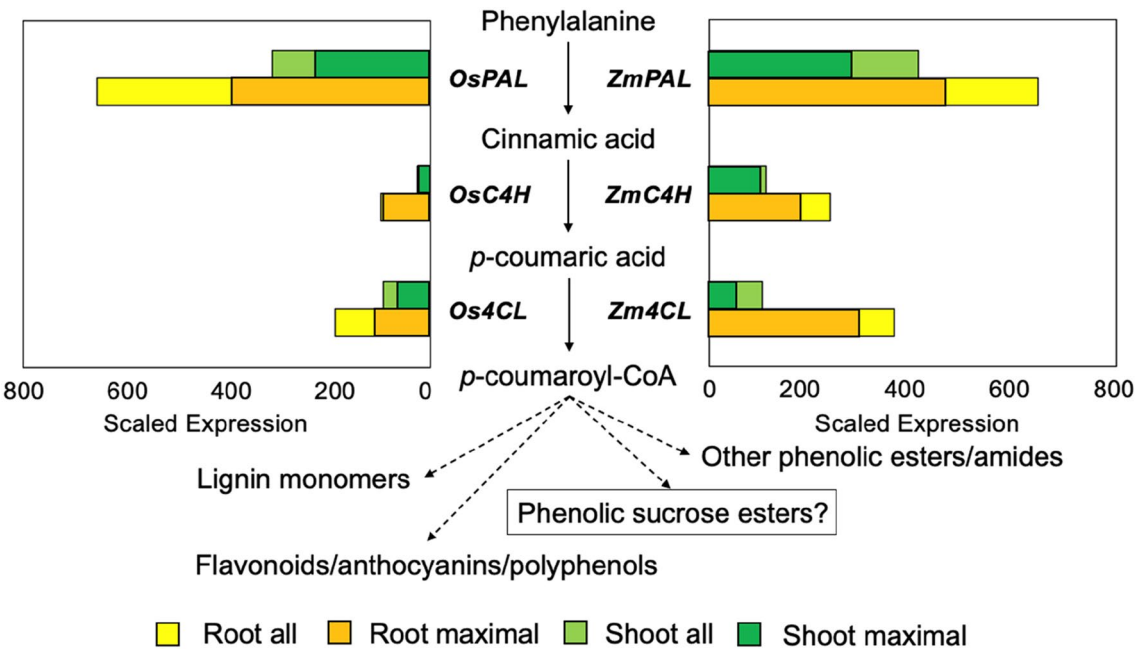

Fig. 4 Organ-specific expression of general phenylpropanoid biosynthetic genes in maize and rice seedlings. Scaled expression level of all (yellow/light green) or the single maximally expressed (orange/dark green) putative phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate:CoA ligase (4CL) genes in seedling roots and shoots are plotted. Gene expression levels in maize and rice were obtained from qTeller (qteller.maizegdb.org) and the IC4R Expression Database (expression.ic4r.org), respectively

heterostrophus, but mechanical wounding alone was insufficient to elicit this response (Zhou et al. 2019b). The observed pathogen-inducibility of PSEs suggested that this class of specialized metabolites may be regulated by classic stress-related phytohormones. Indeed, natural variation in smilaside A and smiglaside C content in maize has been associated with the expression level of an ethylene signaling pathway gene, *ETHYLENE INSENSITIVE 2* (*EIN2*; Zhou et al. 2019b). *In planta* manipulation of ethylene content and downstream responses can lead to significant changes in the abundance of these two compounds (Zhou et al. 2019b). Although these results suggest that PSEs may also be regulated by other stress-related phytohormones such as jasmonic acid and salicylic acid, so far there are no experimental data supporting this hypothesis.

Biosynthesis of phenolic sucrose esters can be inferred with a combination of biochemical hypotheses and correlative analysis of multi-omics data

Despite the wide taxonomic distribution of PSEs, no enzymes catalyzing the biosynthesis of these metabolites have been identified. Nevertheless, the structural similarity of PSEs to other phenolic acid esters suggests that different members of the same class of hydroxycinnamoyl transferases (HCTs) may be responsible for the formation of the ester bond between the phenolic acid moiety and the sucrose backbone (D'Auria et al. 2006). As more than 50% of plant-derived PSEs are acetylated, the acetyltransferases catalyzing these modifications should also be considered as a part of the biosynthetic pathway (Fig. 5). In solanaceous plants that produce acylsugars, including sucrose with acyl side chains of various lengths,

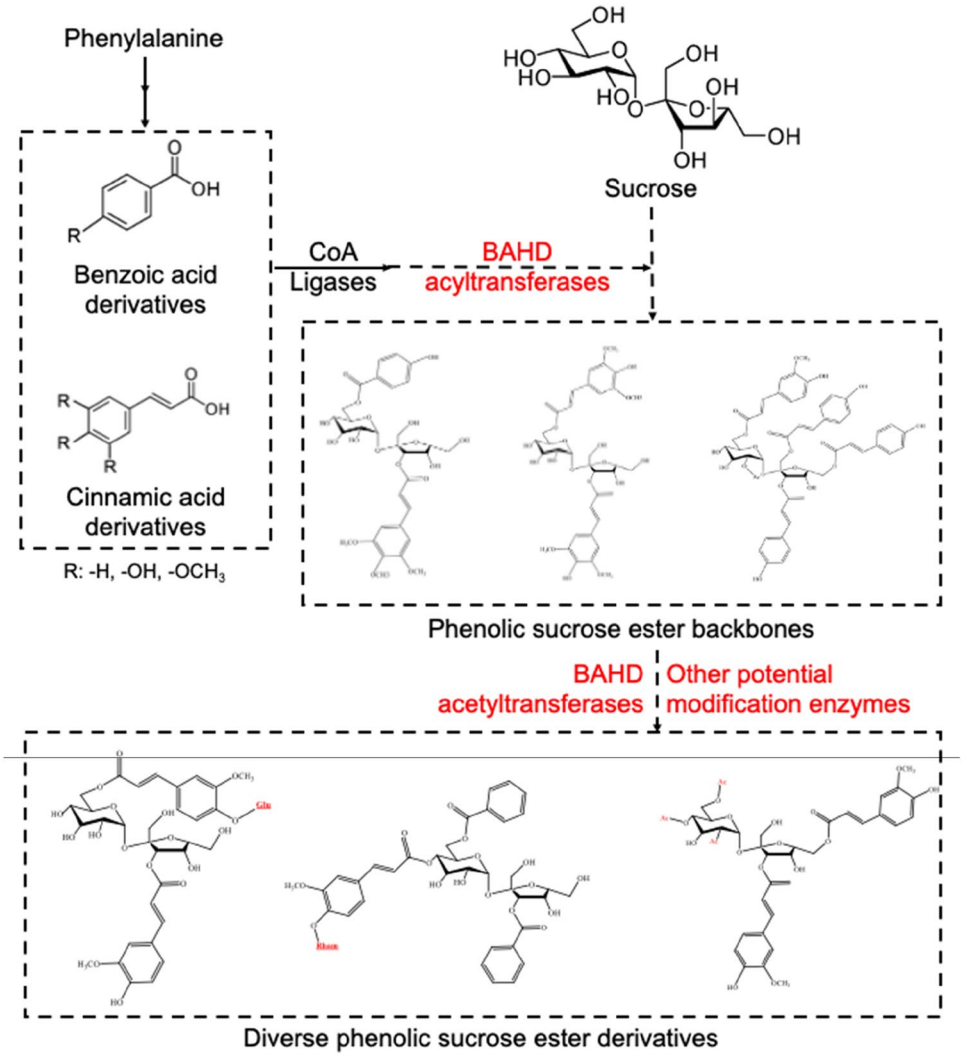

Fig. 5 Hypothetical core biosynthetic pathway of phenolic sucrose esters. Known biosynthetic steps shared with other specialized metabolic pathways are shown as solid arrows, whereas hypothetical steps specific to PSE biosynthesis are dashed. Enzymes shown in red are inferred based on reported compound structures. *Glu* glucoside; *Rham* rhamnoside

acetylation is catalyzed by BAHD acyltransferases, specifically acylsugar acetyltransferases (ASATs; Schilmiller et al. 2012). Given the structural similarity of acylsugars and PSEs, we hypothesize that the acetylation of PSEs is also catalyzed by one or more BAHD acetyltransferases, possibly related to the solanaceous ASATs. We further hypothesize that the acetylation steps should occur after the esterification of phenylpropanoids and the sucrose molecule, as non-acetylated PSEs are widely distributed in angiosperms.In some rare cases, PSEs can be further modified with glycosyl or acetyl groups on the phenolic acid moiety. Since the structural features of the phenolic acid residues are usually required for the proper function of HCTs, it is more likely that these modifications would occur after the esterification with the sucrose backbone (Eudes et al. 2016).

The biochemical hypotheses derived from known biosynthetic pathways of other phenolic acid esters and acylsugars strongly suggest that BAHD acyltransferases (including HCTs) are main players in PSE biosynthesis. However, this class of enzymes is encoded by one of the largest and most diverse gene families in angiosperms, making it impractical to experimentally identify and test genes that participate in PSE biosynthesis (D'Auria et al. 2006). With accumulating reports of PSEs in staple crop species with rich omics datasets, we propose that a correlative analysis method of multi-omics data can be applied to narrow down the list of candidate PSE biosynthetic genes. In maize, where PSEs were recently identified, the abundance of these compounds varies significantly among inbred lines and in different tissue types (Zhou et al. 2019b). Published transcriptomes from different maize genotypes and tissue types identify a smaller subset of maize BAHD acyltransferases with expression patterns that are correlated with PSE abundance (Fig. 6; Supplemental Table 4). This demonstrates the feasibility of a multi-omics analysis approach to identify candidate PSE biosynthetic genes for experimental validation. Hence, it would be possible to identify a shortlist of candidate genes by collecting additional transcriptomic and metabolomic data from the same set of biological samples. In addition, genetic mapping and association studies have recently emerged as a powerful tool in dissecting metabolic pathways in crop species (Miehls et al. 2013; Handrick et al. 2016; Ding et al. 2020). *ZmEIN2*, a regulatory gene affecting the abundance of smilaside A and smiglaside C in maize, was identified by genetic mapping using sets of recombinant inbred lines and near-isogenic lines derived from the B73 and Mo17 inbred lines (Zhou et al. 2019b). Therefore, further genetic mapping and genome-wide association studies using species with well-established germplasm and genetic resources could facilitate the identification of enzymes in the PSE biosynthetic pathway.

Biological functions and potential applications of phenolic sucrose esters

Since their initial identification in the 1980s, PSEs have been hypothesized to be the active ingredient in several traditional medicinal plants, including *Polygala tenuifolia* (yuan zhi), *Sparganium stoloniferum* (hei san leng), and *Smilax glabra* (tu fu ling). Although plant extracts rich in PSEs have been used as alternative treatment for symptoms ranging from common cold to insomnia, controlled experiments with isolated PSEs have mainly involved their anti-oxidative, cytotoxic, and anti-inflammatory activities (reviewed in Panda et al. 2011). For example, PSEs isolated from *Smilax bracteata* have shown significant free radical scavenging activities (Zhang et al. 2008). Vanicoside B, a PSE found in various *Polygonum* species, has significant inhibitory effect on mouse skin tumors, as well as on the activity of proliferation-related protein kinase C family proteins (Zimmermann and Sneden 1994; Takasaki et al. 2001a). Furthermore, different coumaroylsucrose derivatives isolated from *Bidens parviflora* could suppress inflammatory responses by inhibiting histamine release (Wang et al. 2003). Since other plant phenolics frequently have been associated with similar biological activities, it is tempting to hypothesize that the PSEs may enhance these activities by condensing multiple phenolic moieties onto a shared sucrose backbone. In support of this hypothesis, PSEs with more attached phenolic moieties exhibited stronger antioxidative activity in an in vitro assay (Panda et al. 2012a). Yet, some PSEs have demonstrated novel biological activities such as glucosidase and acetylcholinesterase inhibitory effects that are not found for the phenolic moieties contained in their free forms (Fan et al. 2010). It also has been postulated that the acetylation could further enhance PSE bioactivity by promoting the hydrophobicity and hence membrane permeability of the molecules (Panda et al. 2012a). However, multiple experiments with PSEs and structurally-related phenylpropanoid glycerol glucosides recently refuted this hypothesis, instead suggesting that acetylation may suppress PSE bioactivity (Zhou et al. 2019b; Murray et al. 2019). As multi-acetylation is common for PSEs, it is possible that the structure–activity relationship between acetylation and different bioactivities of PSEs is more complex than a simple linear relationship, such that PSEs acetylated to different degrees are optimal for different biological functions.

The recent discovery and investigation of PSEs in poaceous crop species have provided an agro-ecological scenario for future research on these compounds. In addition to the pathogen-inducibility discussed above, smilaside A isolated from maize can inhibit the in vitro growth of *Fusarium graminearum* (Zhou et al. 2019b). In another study, transgenic maize callus overexpressing a chalcone

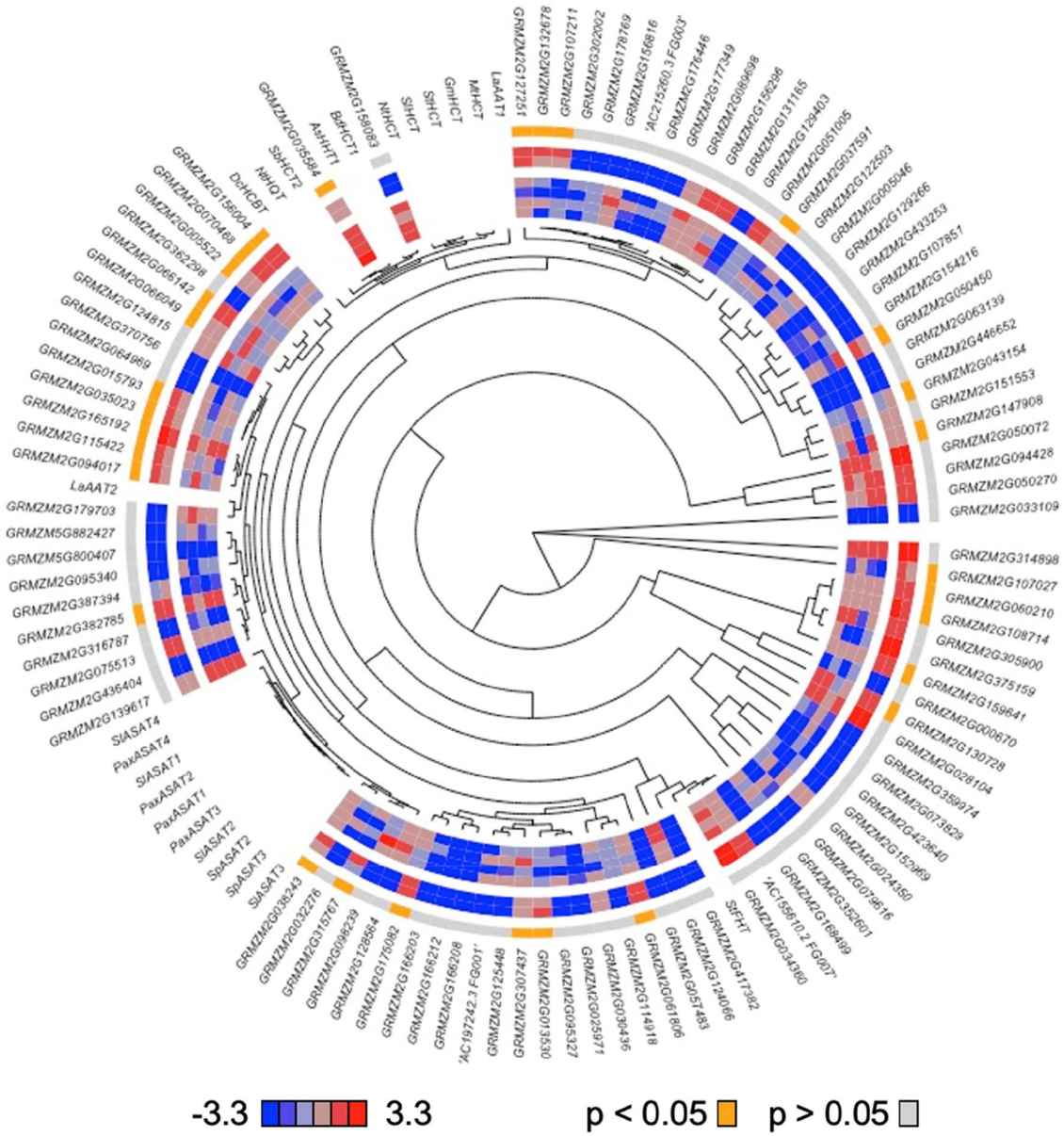

Fig. 6 Candidate phenylpropanoid sucrose ester biosynthetic gene mining in *Zea mays* based on published transcriptomic datasets. Amino acid sequences of all predicted BAHD acyltransferase-encoding genes in *Zea mays* B73 Refgen v3 were aligned to characterized BAHD acyltransferases from other plant species (listed in Supplemental Table 4) to build a gene phylogeny. The expression levels of genes in B73 seedling roots, Mo17 seedling roots, B73 shoots, and Mo17 shoots are based on qTeller data (qteller.maizegdb.org), scaled into discrete categories, and shown in concentric rings from inside to outside, respectively. Scaled expression of each gene in B73 and Mo17 seedling roots, measured in a separately published 3′ RNAseq experiment (Zhou et al. 2019a) and corresponding comparison statistics from Student's *t*-tests, are shown in the three outer rings

isomerase 3-like gene had elevated PSE levels, as well as enhanced resistance against insect herbivores and fungal pathogens (Dowd et al. 2018). In transgenic sorghum lines with decreased lignin content, the increase of soluble phenolics, including PSEs, may help to maintain the wildtype-level resistance to various fungal pathogens and insect herbivores in these plants (Dowd and Sattler 2015; Funnell-Harris et al. 2017) This experimental evidence, albeit preliminary, supports the hypothesis that PSEs are important components of maize defense against fungal pathogens.

The in vitro fungistatic and other bioactive effects of PSEs probably are linked to the antioxidative and antibiotic properties of the phenolic moieties. For example, direct application of phenolic acids inhibited in vitro growth of phytopathogens including *Fusarium graminearum* and

Phytophthora nicotianae (Ponts et al. 2011; Zhang et al. 2020). It is hence interesting to investigate how and why ferulate- and other phenolic moiety-containing PSEs could affect the bioactivities of free phenolics. We hypothesize that the sucrose moiety could enhance the hydrophilicity, as well as serving as a carrier to deliver multiple phenolic molecules in a conjugated form. Additionally, the function of PSEs in plant defense may go beyond the innate biochemical properties of the molecules. Ferulic acids, for example, crosslink and reinforce plant cell walls by generating ferulate-polysaccharide-lignin complexes, which are important for cell wall integrity and plant defense against fungal pathogens (Buanafina 2009). Hence, it is reasonable to speculate that PSEs, which often contain one or more hydroxycinnamoyl moieties, can perform a similar function, which could not be studied in vitro. Further confirmation of PSE functions in plant defense will require *in planta* evidence based on stable and specific genetic manipulation, which in turn depends on the elucidation of a PSE biosynthetic pathway in a genetically tractable crop species such as maize or rice. Such experiments will pave the way for the development of disease-resistant crop cultivars with modulated PSE composition, as well as for engineering PSE biosynthesis in heterologous systems.

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Authors' contributions RD and SZ summarized literature and published data, and performed re-analyses. All authors collaboratively drafted the manuscript.

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Availability of data and materials All data used for analyses in this publication were obtained from the public domain.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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