



Review

Plant Polyketide Synthases: A fascinating group of enzymes

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ABSTRACT

The Polyketide Synthases (PKSs) are condensing enzymes which form a myriad of polyketide compounds. Several PKSs have been identified and studied in plants. This mini-review summarizes what is known about plant PKSs and some of their aspects such as specificity, reaction mechanisms, structure, as well as their possible evolution are highlighted.

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1. Introduction

The polyketide natural products are one of the largest and most diverse groups of secondary metabolites. They are formed by a myriad of different organisms from prokaryotes to eukaryotes. Antibiotics and mycotoxins produced by fungi and actinomycetes, and stilbenoids and flavonoids produced by plants are examples of polyketide compounds. They have an important role in medicine, due to their activities such as antimicrobial, anti-parasitic, antineoplastic and immunosuppressive [85,90,118].

2. Polyketide Synthases

The Polyketide Synthases (PKSs) are a group of enzymes that catalyze the condensation of a starter CoA ester, such as acetyl-CoA, with extender CoA esters, such as malonyl-CoA. They are classified according to their architectural configurations as type I, II and III [41,51,106]. The type I describes a system of one or more multifunctional proteins that contain a different active site

for each enzyme-catalyzed reaction in assembly and modification of the polyketide carbon chain. They are organized into modules, containing at least acyltransferase (AT), acyl carrier protein (ACP) and β -keto acyl synthase (β -KS) activities. Type I PKSs are sub-grouped as iterative or modular; usually present in fungal or bacterial systems [70,76]. The type II is a system of individual enzymes that carry a single set of iteratively acting activities. A minimal set consists of two ketosynthase units (α - and β -KS) and an ACP, which serves as an anchor for the growing polyketide chain. Additional PKS subunits such as ketoreductases, cyclases or aromatases define the folding pattern of the polyketo intermediate and further post-PKS modifications, such as oxidations, reductions or glycosylations are added to the polyketide [48,87]. The only known group of organism that employs type II PKS systems for polyketide biosynthesis is soil-borne and marine Gram-positive actinomycetes. The type III is present in bacteria, plants and fungi [22,23,44,101]; they are essentially condensing enzymes that lack ACP and act directly on acyl-CoA substrates.

Here, we will review the type III PKSs from plants; as they play a major role in the biosynthesis of important plant compounds.

3. Plant Polyketide Synthases

Several type III PKSs have been found in plants and all of them participate in the biosynthesis of secondary metabolites (Table 1 and Fig. 1): chalcone synthase (CHS), 2-pyrone synthase (2-PS), stilbene synthase (STS), bibenzyl synthase (BBS), homoeriodictyol/eriodictyol synthase (HEDS or HvCHS), acridone synthase (ACS), benzophenone synthase (BPS), phlorisovalerophenone synthase (VPS), isobutyrophenone synthase (BUS), coumaroyl triacetic acid

Abbreviations: ACP, acyl carrier protein; ACS, acridone synthase; acyl-CoA, acyl derivative of coenzyme A; ALS, aloesone synthase; AT, acyltransferase; BAS, benzalacetone synthase; CHS, chalcone synthase; CTAS, coumaroyl triacetic acid synthase; FAS, fatty acid synthase; KS, keto acyl synthase; OKS, octaketide synthase; PKS, polyketide synthase; 2-PS, 2-pyrone synthase; PstrCHS2, C-methylchalcone synthase; STS, stilbene synthase; STCS, stilbene carboxylate synthase; VPS, phlorisovalerophenone synthase.

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Table 1
Examples of plant polyketide synthases, preferred substrates and reaction products.

Enzyme	Substrates (starter, extender, no. condensations)	Type of ring closure, ring type	Product ^a	Plant species	References
<i>None cyclization reaction</i>					
Benzalacetone synthase (BAS), EC 2.3.1.-	<i>p</i> -Coumaroyl-CoA, malonyl-CoA (1X)		Benzalacetone (1)	<i>Rubus idaeus</i> , <i>Rheum palmatum</i>	[4,12,27,124]
	Feruloyl-CoA, malonyl-CoA (1X)		Methoxy-benzalacetone (2)		
<i>One cyclization reaction</i>					
Benzalacetone synthase (BAS), EC 2.3.1.-	<i>N</i> -methylanthraniloyl-CoA (or anthraniloyl-CoA), malonyl-CoA (or methyl-malonyl-CoA) (1X)	-, Heterocyclic	4-Hydroxy-2(1 <i>H</i>) quinolones (3)	<i>R. palmatum</i>	[1]
<u>CTAS-type</u>					
C-methylchalcone synthase (PstrCHS2)	Diketide-CoA, methyl-malonyl-CoA (1X)	Lactonization, heterocyclic	Methyl-pyrone (4)	<i>Pinus strobus</i>	[98]
2-pyrone synthase (2-PS)	Acetyl-CoA, malonyl-CoA (2X)		Triacetic acid lactone (TAL) (5)	<i>Gerbera hybrida</i>	[36,55]
<i>p</i> -Coumaroyltriacetic acid synthase (CTAS)	<i>p</i> -Coumaroyl-CoA, malonyl-CoA (3X)		<i>p</i> -Coumaroyltriacetic acid lactone (6)	<i>Hydrangea macrophylla</i> <i>var. thunbergii</i>	[17]
<u>CHS-type</u>					
Chalcone synthase (CHS), EC 2.3.1.74	<i>p</i> -Coumaroyl-CoA, malonyl-CoA (3X)	Claisen, aromatic	Naringenin chalcone (7)	<i>Medicago sativa</i>	[23,40]
Phlorisovalerophenone synthase (VPS), EC 2.3.1.156	Isovaleroyl-CoA, malonyl-CoA (3X)		Phlorisovalerophenone (8)	<i>Humulus lupulus</i>	[78,80]
Isobutyrophenone synthase (BUS)	Isobutyryl-CoA, malonyl-CoA (3X)		Phlorisobutyrophenone (9)	<i>Hypericum calycinum</i>	[63]
Benzophenone synthase (BPS), EC 2.3.1.151	<i>m</i> -Hydroxybenzoyl-CoA, malonyl-CoA (3X)		2,3',4,6-Tetrahydroxybenzophenone (10)	<i>Centaurium erythraea</i>	[25]
	Benzoyl-CoA, malonyl-CoA (3X)		2,4,6-Trihydroxybenzophenone (11)	<i>Hypericum androsaemum</i>	[66]
Acridone synthase, EC 2.3.1.159 (ACS)	<i>N</i> -methylanthraniloyl-CoA, malonyl-CoA (3X)		1,3-Dihydroxy- <i>N</i> -methylacridone (12)	<i>Ruta graveolens</i> , <i>Huperzia serrata</i>	[60,103,115]
Homoeriodictyol/eriodictyol synthase (HEDS or HvCHS)	Feruloyl-CoA, malonyl-CoA (3X) Caffeoyl-CoA, malonyl-CoA (3X)		Homoeriodictyol (13) Eriodictyol (14)	<i>Hordeum vulgare</i>	[23,30]
<u>STS-type</u>					
Stilbene synthase (STS), EC 2.3.1.95	<i>p</i> -Coumaroyl-CoA, malonyl-CoA (3X)	Aldol, aromatic	Resveratrol (15)	<i>Arachis hypogaea</i> , <i>Pinus sylvestris</i>	[21,93,102]
Pinosylvin synthase, EC 2.3.1.146	Cinnamoyl-CoA, malonyl-CoA (3X)		Pinosylvin (16)	<i>P. sylvestris</i> , <i>Pinus strobus</i>	[43,84,91]
Bibenzyl synthase (BBS)	Dihydro- <i>m</i> -coumaroyl-CoA, malonyl-CoA (3X)		3,3',5-Trihydroxybibenzyl (17)	<i>Phalaenopsis</i> sp., <i>Bletilla striata</i>	[81,86]
Biphenyl synthase (BIS)	Benzoyl-CoA, malonyl-CoA (3X)		3,5-Dihydroxybiphenyl (18)	<i>Sorbus aucuparia</i>	[67]
Stilbenecarboxylate synthase (STCS)	Dihydro- <i>p</i> -coumaroyl-CoA, malonyl-CoA (3X)	Aldol without decarboxylation, aromatic	5-Hydroxylunularic acid (19)	<i>H. macrophylla</i> , <i>Marchantia polymorpha</i>	[35,97]
<i>More than 2 cyclization reactions</i>					
<u>Miscellaneous type</u>					
Pentaketide chromone synthase (PCS)	Acetyl-CoA, malonyl-CoA (4X)	-, Heterocyclic or aromatic	5,7-Dihydroxy-2-methylchromone (20)	<i>Aloe arborescens</i>	[7]
Hexaketide synthase (HKS)	Acetyl-CoA, malonyl-CoA (5X)		6-(2',4'-Dihydroxy-6'-methylphenyl)-4-hydroxy-2-pyrone (21)	<i>Drosophyllum lusitanicum</i> , <i>Plumbago indica</i>	[59,104]
Aloesone synthase (ALS)	Acetyl-CoA, malonyl-CoA (6X)		Aloesone (22)	<i>R. palmatum</i>	[8]
Octaketide synthase (OKS)	Acetyl-CoA, malonyl-CoA (7X)		SEK4 (23) and SEK4b (24) (octaketides)	<i>A. arborescens</i>	[2]

-, undefined.

^a In some cases the products in vitro bear little relationship with the compounds found in the plant. It is not clear if the reactions in vivo and in vitro are the same and further tailoring reactions can play an important role in directing the flux of a pathway in a certain direction.

synthase (CTAS), benzalacetone synthase (BAS), C-methylchalcone synthase (PstrCHS2), anther-specific chalcone synthase-like (ASCL) and stilbene carboxylate synthase (STCS) are some examples from this group [15,20,23,35,63,120,122]. As CHS and STS are the most studied enzymes, this group is often called the family of the CHS/STS type. Analyzing the sequences reported for type III PKSs of plant origin a 46–95% amino acid sequence identity is observed [11,23,95,104,115]. They utilize a variety of different starter substrates ranging from aliphatic-CoA to aromatic-CoA substrates, from small (acetyl-CoA) to bulky (*p*-coumaroyl-CoA) substrates or from polar (malonyl-CoA) to nonpolar (isovaleroyl-CoA) substrates giving the plants an extraordinary functional diversification.

3.1. Type of cyclization reaction

Divergences by the number of condensation reactions (polyketide chain elongation), the type of the cyclization reaction and the starter substrate are characteristic of the plant PKSs [96]. Based on the mechanism of the cyclization they are classified as CHS-, STS- and CTAS-type (Fig. 2).

In the CHS-type the intramolecular cyclization from C6 to C1 is called Claisen condensation; this mechanism for the carbon-carbon bond formation is not only used for the biosynthesis of polyketides, but also for fatty acids [46]. In the STS-type the cyclization is from C2 to C7, with an additional decarboxylative loss of the C1 as CO₂, this reaction is an Aldol type of condensation. In the CTAS-type

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