

Advances in Polyketide Related Biosynthesis Using Engineered *Yarrowia lipolytica*

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Abstract. *Yarrowia lipolytica*, a robust oleaginous non-conventional yeast, exhibits unique advantages for natural product biosynthesis due to its high endogenous acetyl-CoA and malonyl-CoA fluxes, broad substrate tolerance, mature genetic tools and superior biosafety. Polyketides, synthesized by polyketide synthases (PKSs), are structurally diverse high-value compounds with extensive pharmaceutical and industrial applications. Attributing to its inherent lipid metabolism, *Y. lipolytica* serves as a superior chassis for polyketide synthesis compared with traditional yeast and bacterial hosts. This review summarizes recent progress in PKS pathway engineering in *Y. lipolytica*, covering the biosynthesis and optimization of representative type I and type III polyketides, including 6-MSA, TAL and the unnatural polyketide HHEP. The metabolic engineering strategies for PKS-derived phenylpropanoids, such as resveratrol and naringenin, are also discussed. Special emphasis is given to the metabolic interplay between heterologous PKS pathways and endogenous lipid metabolism, highlighting the precursor competition and flux redistribution that determine final product yields. Key challenges and prospective optimization strategies are also discussed to facilitate future development of robust *Y. lipolytica* cell factories for efficient polyketide bioproduction.

Keywords: *Yarrowia Lipolytica*, Polyketides, polyketide synthases, lipid metabolism

1. Introduction

Yarrowia lipolytica, a non-conventional lipid-utilizing yeast, is emerging as an industrial workhorse of growing interest. Owing to its generally recognized safety, unique intrinsic properties, and well-developed engineering tools, *Y. lipolytica* harbors great potential in biosynthesizing bioactive natural products.

Initially isolated from oily and protein-rich environments, *Y. lipolytica* exhibits an exceptionally active lipid-related metabolisms. Therefore, an ample supply of precursors—namely acetyl-CoA and malonyl-CoA—endows an innate potential for supporting biosynthetic pathways [1]. Since its oleaginous nature guarantees an innate capacity to assimilate, accumulate and secrete hydrophobic compounds [2], *Y. lipolytica* presents innate strengths toward industrial deployment including straightforward downstream purification and substrate versatility.

Beyond these inherent gifts, the past few decades have witnessed developments of synthetic biology tools that realize the biotechnological potential of *Y. lipolytica*. A rich molecular toolbox is

now available, including CRISPR-Cas9 for precise genome editing to its fully sequenced chromosomes, a panel of constitutive and inducible promoters for fine-tuning gene expression, and advanced systems such as ZETA (a CRISPR-based activation system) [3]. Most industrial strains have been completely sequenced, providing a solid foundation for rational metabolic engineering. Building upon its innate capacity to harness various substrates—including starch, cellulose, xylan, and inulin via hydrolytic secretome engineering [4, 5]—researchers have engineered metabolic pathways starting from substrate utilization to boost the biosynthesis of terpenoids, secreted proteins, and lipids [6]. These engineering efforts collectively position *Y. lipolytica* as a versatile and powerful chassis for sustainable biomanufacturing.

2. Research progress of *Yarrowia lipolytica* in natural product and polyketide biosynthesis

2.1. Natural advantages of *Yarrowia lipolytica* for polyketide synthesis

Recent advances have significantly expanded the biotechnological applications of *Y. lipolytica*, establishing it as a premier non-conventional yeast chassis. In terpenoid production, titers have been pushed to unprecedented levels through sophisticated pathway engineering. For instance, the diterpenoid sclareol reached 3.3 g/L in shake flasks and 12.9 g/L in 5 L bioreactors by overexpressing a heterologous geranylgeranyl diphosphate synthase (tPaGGPPS) and fusing biosynthetic enzymes [7]. Furthermore, the first *de novo* synthesis of the phenolic monoterpenes thymol and carvacrol was achieved, with titers reaching 61.31 mg/L in bioreactors [8]. Impressive titers have also been achieved for other terpenoids; for example, Chen et al. reported a landmark 2.55 g/L of zeaxanthin, marking the first *de novo* biosynthesis of 3-hydroxy- β -ionone [9]. This record was quickly broken by Hou's team, who achieved a current record of 6.9 g/L of zeaxanthin in fed-batch fermentation [10]. These achievements are supported by the development of new chassis strains with triple autotrophies and deletions of up to five protease genes, enabling high-level production that does not rely solely on multi-copy expression strategies.

2.2. Research progress of polyketide synthesis

Polyketides are a large family of natural products biosynthesized by polyketide synthases (PKSs) through successive Claisen condensations of simple acyl-CoA building blocks. This process produces a characteristic poly- β -ketone backbone that undergoes variable post-assembly modifications—including cyclization, reduction, and glycosylation—to generate diverse structural scaffolds. Key strategies recently developed at the forefront of polyketide engineering include the modular refactoring of biosynthetic gene clusters (e.g., achieving a 15-fold increase in doxorubicin production) [11], the construction of high-performance chassis hosts tailored for polyketide biosynthesis (e.g., *Streptomyces* Chassis 2.0 boosting oxytetracycline yield by 370%) [12], and the rational engineering of rate-limiting enzymes uniquely suited to polyketide synthases (e.g., an EryF mutant increasing erythromycin precursor yield by 4-fold).

The PKS pathways in *Y. lipolytica* have been harnessed not only for the combinatorial synthesis of diverse polyketides—ranging from the simple type III PKS product triacetic acid lactone (TAL) to complex type I PKS products such as 6-MSA and the *Fusarium*-derived bostrycoidin—but they also function as a powerful metabolic probes to dissect the host's central carbon and lipid metabolic networks. Given that *Y. lipolytica* is an oleaginous yeast with a high inherent flux of acetyl-CoA and malonyl-CoA (the primary building blocks for both lipid accumulation and polyketide extension),

engineering PKS pathways has become a strategy to redirect these precursors away from neutral lipids and toward value-added chemicals in this host [13].

This review will cover recent progress in engineering for the biosynthesis of typical type I and type III polyketides, newly discovered unnatural polyketides, and type III PKS-derived phenylpropanoid products, as well as the metabolic interplay between PKS pathways and endogenous lipid and polyunsaturated fatty acid metabolism.

3. Advances in the biosynthesis of typical polyketides in engineered *Yarrowia lipolytica*

3.1. Biosynthesis optimization of type I polyketide: 6-Methylsalicylic acid (6-MSA)

6-Methylsalicylic acid (6-MSA) is a simple polyketide secondary metabolite biosynthesized primarily by fungi via the iterative type I polyketide synthase 6-MSAS, using one acetyl-CoA and two malonyl-CoA units. *Y. lipolytica* constitutes a superior heterologous production host because its native central metabolism intrinsically generates a high flux toward both acyl-CoA precursors, directly matching this biosynthetic demand. Traditionally, 6-MSA was best produced in *S. cerevisiae*, cultivation achieved a final titer of 2.01 g/L and completely converted to downstream products [14]. By integrating multiple copies of 6-MSAS and introducing PPTase, the biosynthesis of 6-MSA in *Y. lipolytica* yielded significantly higher productivity. Attempts to enhance β -oxidation to obtain additional acetyl-CoA precursors from free fatty acids degradation by overexpressing the involved enzymes (TGL4 and AOX2), had a negligible effect [15]. In another study, metabolic optimization including ACC1 overexpression was applied to strengthen acetyl-CoA-to-malonyl-CoA conversion, and disruption of DGA increased intracellular malonyl-CoA by inhibiting the malonyl-CoA-consuming pathway of triacylglycerol synthesis, which produced additional precursors for PKS construction [16]. Ultimately, the yield of 6-MSA reached 3.93 g/L in flask cultivation.

3.2. High-efficiency synthesis of simple type III polyketide: triacetic acid lactone (TAL)

Triacetic acid lactone (4-hydroxy-6-methyl-2-pyrone) (TAL) is a natural compound of polyketide origin and has a wide range of industrial applications; it serves as a precursor in the chemical synthesis of acetylacetone used in fuel additives, sorbic acid used in food additives, phloroglucinol used to synthesize heat-stable energy material 1,3,5-triamino-2,4,6-trinitrobenzene (TATB), and resorcinol used to formulate resins and adhesives. Conventionally, 2-pyrone synthase is introduced into engineered strains to produce TAL. To enhance the process, PEX10 was overexpressed to promote β -oxidation for acetyl-CoA generation and ACC1 was overexpressed to convert acetyl-CoA to malonyl-CoA, achieving TAL titer of 8.6 ± 0.8 g/L in a 3 L bioreactor using nitrogen-limited media [17]. However, the results were significantly inferior to the landmark 2018 study that achieved 35.9 g/L via acetate feeding and high-glucose fermentation, since it did not apply similar productive fermentation conditions [18].

Y. lipolytica's ability to utilize a variety of carbon sources beyond glucose can be selectively enhanced for microbial cultivation of certain products. By introducing xylose reductase and dehydrogenase from *Scheffersomyces stipitis* — a method more productive than overexpressing native genes — researchers obtained a significantly higher TAL yield of 1.61 g/L from xylose, compared with only 0.71 g/L from glucose in shake flasks. The superior performance on xylose attributes to its metabolism through the pentose phosphate pathway, which generates more NADPH — a critical cofactor for TAL synthesis — than glucose through glycolysis [5].

3.3. Discovery and biosynthesis of novel unnatural polyketide HHEP

The PKS pathway also exhibits potential for producing previously undiscovered products. Researchers recently synthesized a new-to-nature polyketide 4-hydroxy-6-hydroxyethyl-2-pyrone (HHEP) during attempts to optimize TAL production via 2-pyrone synthase (2-PS). The AMM pathway, which converts L-aspartate to malonyl-CoA, generates an intermediate called malonate semialdehyde (MalSA). MalSA is subsequently transformed into 3-HP by the endogenous enzyme HBD1. 3-HP is then activated to 3-HP-CoA, which can be condensed by 2-PS into HHEP. The total titer of polyketides in a 1 L bioreactor was 6.96 g/L, with HHEP alone reaching 5.37 g/L. Additionally, the total lipid titer increased by 17.0% (and odd-chain fatty acids by 25.3%) because the AMM pathway enriched intracellular propionyl-CoA and malonyl-CoA pools [19].

4. Type III PKS-derived phenylpropanoid natural products biosynthesis

4.1. PKS III-dependent resveratrol synthesis and targeted metabolic modification

Resveratrol is a plant-derived stilbenoid synthesized via the type III polyketide synthase (PKS) pathway, in which stilbene synthase (STS) acts as a specialized PKS enzyme that catalyzes the condensation of one 4-coumaroyl-CoA molecule with three malonyl-CoA molecules. Analogous to other PKS-derived natural products, resveratrol biosynthesis originates from phenylalanine or tyrosine. The two aromatic amino acids are converted to *p*-coumaric acid (*p*-CA) and subsequently into the unstable intermediate 4-coumaroyl-CoA. Iterative decarboxylative condensation of this intermediate represents the core chemical characteristics of the PKS pathway.

In previous *Y. lipolytica* studies, resveratrol biosynthesis based on the STS-catalyzed condensation of *p*-coumaroyl-CoA and malonyl-CoA received only modest production performance. Aiming to increase malonyl-CoA supply, prior attempts introduced *Arabidopsis thaliana* AtACC2 to convert endogenous acetyl-CoA into malonyl-CoA, alongside with the co-expression of *Bradyrhizobium diazoefficiens* BdMatB and BdMatC. Nevertheless, these strategies failed to realize high resveratrol titers even while incorporating exogenous malonate supplementation [20].

Unlike previous studies, Liu et al. adopted multiple targeted metabolic modifications to efficiently boost resveratrol synthesis [21]. First of all, the native pentose phosphate pathway (PPP) was bypassed by heterologously expressing *Clostridium acetobutylicum* fructose-6-phosphate phosphoketolase (CaFPK). This heterologous route elevates E4P supply, thereby strengthening the biosynthesis of aromatic amino acid precursors. A rigid EAAAK linker was then applied to fuse Pc4CL1 (4-coumarate-CoA ligase) and VvSTS (stilbene synthase). Consequently, the substrate channeling reduced the diffusion and degradation of unstable 4-coumaroyl-CoA, improved *p*-CA conversion efficiency, and facilitated resveratrol synthesis. In addition, the DGA1 gene was knocked out to reduce lipid metabolic competition and further increase intracellular malonyl-CoA availability.

Collectively, these systematic metabolic optimizations enabled the engineered strain to accumulate resveratrol up to 819.1 mg/L in shake-flask cultivation. Subsequent fermentation parameter optimization in a scaled-up bioreactor further elevated the product titer to a maximum of 22.5 g/L. This remarkable titer enhancement substantially outperforms the outcomes documented in earlier relevant studies.

4.2. Biosynthetic optimization of naringenin and acacetin derivatives

Naringenin is a flavonoid predominantly found in citrus fruits, recognized for its potent antioxidant and anti-inflammatory properties. Produced through a conserved seven-step biosynthetic route using *p*-coumaric acid and 4-coumaroyl-CoA alongside chalcone synthase, and chalcone isomerase, naringenin serves as the immediate precursor for more than 8 000 diverse flavonoid molecules including apigenin, acacetin, eriodictiol, and taxifolin [22]. Naringenin is synthesized from L-tyrosine via its deamination to *p*-coumaric acid by TAL, followed by activation to *p*-coumaroyl-CoA by 4CL, and then a type III PKS (CHS) condenses it with three malonyl-CoAs to form naringenin chalcone, which finally cyclizes to naringenin. To boost precursor availability, the researchers relieved L-tyrosine feedback repression by overexpressing mutant resistance alleles (ARO4^{K221L}) and enhancement of β -oxidation by over-expressing PEX10, resulting in a titer of 124 mg/L in flask and 898 mg/L in 3 L bioreactor¹⁷. In 2024, Park et al. reported a titer of up to 606.9 mg/L in shake flasks by introducing ARO2 and ARO7^{G139S}, including strategies such as deleting the competing gene 4HPPD to minimize byproduct formation, redirecting malonyl-CoA by FAS1 downregulation, and enhancing E4P supply through TKL1 overexpression [23].

5. Metabolic crosstalk between PKS pathway and endogenous lipid metabolism

PKS-mediated metabolic regulation is tightly associated with intracellular acetyl- and malonyl-CoA flux, which represents the core metabolic advantage of *Y. lipolytica*. Modulation of the PKS pathway significantly interferes with other metabolic routes, especially lipid metabolism. This crosstalk is largely mediated by fatty acid β -oxidation, which degrades lipids into acetyl-CoA, thereby replenishing the acetyl-CoA pool and, via carboxylation, the malonyl-CoA pool. Since both acetyl-CoA and malonyl-CoA are direct precursors for PKS-driven polyketide synthesis, any perturbation in PKS activity or lipid turnover can reciprocally reshape lipid homeostasis and polyketide accumulation.

By refactoring the architecture of a heterologous four-gene PKS-like PUFA synthase cluster from myxobacteria using a combination of the minLEU2 promoter, four UAS1B enhancer repeats, 5' introns, and intergenic spacers in a low-producing strain, Dietrich et al. (2023) increased DHA production in *Y. lipolytica* by 16-fold, reaching 17.1% of total fatty acids. Notably, this enhanced DHA biosynthesis depleted intracellular acetyl-CoA and malonyl-CoA pools, with the best-performing strain containing 80% less malonyl-CoA than low-producing strains [24]. Interestingly, another study found that integrating the heterologous PKS cluster PFA3 halted DHA production and induced EPA and DPA synthesis, whereas Mr1 integration boosted tri- and tetra-unsaturated ω -3/ ω -6 species [25]. Both studies concluded that selective substrate processing by engineered PKS clusters consumes acetyl- and malonyl-CoA pools, enhances target polyunsaturated fatty acid production, and alters fatty acid chain-length distribution. Separately, Wei et al. achieved 715.3 mg/L of DHA in shake flasks by engineering a xylose-inducible system that couples xylose utilization with naringenin biosynthesis, enabling xylose to function as both a carbon source and a pathway inducer [26].

6. Conclusions and future perspectives

Table 1. Comparison of polyketide-derived natural product titers obtained from different microbial chassis

product	host	Flask or tube yield	Bio-reactor yield
(2S)-Naringenin	<i>Y. lipolytica</i>	776.3 mg/L	8.65 g/L
	<i>S. cerevisiae</i>	986.2 mg/L	3.42 g/L
	<i>E. coli</i>	474.0 mg/L	3.11 g/L
resveratrol	<i>Y. lipolytica</i>	819.1 mg/L	22.5 g/L
	<i>S. cerevisiae</i>	1155 mg/L	4.10 g/L
TAL	<i>Y. lipolytica</i>	4110 mg/L	35.9 g/L
	<i>P. pastoris</i>	451 mg/L	1.83 g/L

The collective body of research (summarized in Table 1) positions *Y. lipolytica* as a superior non-conventional chassis for natural product biosynthesis, offering distinct advantages over traditional hosts such as *S. cerevisiae* and *E. coli*. This is attributed to its intrinsically high acetyl-CoA and malonyl-CoA flux, derived from an exceptionally active lipid metabolism, providing significant potentials in terms of polyketide production and PKS related products, for acetyl-CoA and malonyl-CoA are key procurers to carbon chain elongation reaction. Its oleaginous nature provides great advantage in PKS product yield and enhances its ability to convert various substrate into material of carbon chain elongation pathway.

Although *Yarrowia lipolytica* already possesses a strong substrate utilization capability, considerable room for improvement remains, as its abundant gene editing tools and excellent protein post-translational modification capabilities enable full overexpression of heterologous genes to construct various substrate utilization pathways. Future research should focus on two core directions: first, resolving the reciprocal flux competition between polyketide synthesis and intracellular lipid accumulation via dynamic metabolic regulation strategies; second, expanding the spectrum of cheap lignocellulosic substrates compatible with engineered PKS pathways. Combined with continuous optimization of modular PKS enzyme engineering and chassis strain modification, *Y. lipolytica* will become an increasingly competitive industrial cell factory for sustainable polyketide biomanufacturing.

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