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Wed. Jul 1, 2026 12:10 PM - 1:00 PM JST | Wed. Jul 1, 2026 3:10 AM - 4:00 AM UTC | Poster 1(4FFoyer+401+402)
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12:10 PM - 1:00 PM JST | 3:10 AM - 4:00 AM UTC

[P03-379] Establishing a microbial platform for orsellinic acid-derived meroterpenoids in *Escherichia coli*

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Keywords：Polyketide、Meroterpenoid、Metabolic engineering、Escherichia coli、Orsellinic acid

Meroterpenoids are a diverse class of natural products that contain a terpenoid moiety as part of their structure and have attracted considerable attention as promising lead compounds for drug discovery because of their broad pharmacological activities. Among them, meroterpenoids containing orsellinic acid, a polyketide compound, as the core structure exhibit remarkable biological activities, including anticancer, anti-HIV, antidiabetic, and anti-inflammatory effects. These orsellinic acid-derived meroterpenoids are naturally produced by *Rhododendron* species and are currently obtained mainly through direct extraction from plants. However, plant-based production suffers from unstable supply due to environmental dependence, variability in compound content, complex purification processes, and conservation concerns. Therefore, microbial fermentation has attracted attention as a promising approach for the sustainable, cost-effective, and stable production of these compounds.

Efficient microbial production of orsellinic acid-derived meroterpenoids requires high-level production of the precursor orsellinic acid. Orsellinic acid is synthesized from acetyl-CoA and malonyl-CoA by polyketide synthase. However, previously reported microbial production levels of orsellinic acid remain low, typically only a few milligrams per liter. In previous studies, metabolic engineering strategies to enhance precursor supply were not sufficiently explored, which likely contributed to the low production titers.

In this study, *Escherichia coli* was metabolically engineered as a host for the *de novo* biosynthesis of orsellinic acid and orsellinic acid-derived meroterpenoids. Introduction of an orsellinic acid synthase resulted in only trace production (1 mg/L), suggesting that insufficient precursor supply was the major bottleneck. To increase intracellular acetyl-CoA and malonyl-CoA availability, competing pathways were knocked down. Metabolome analysis was subsequently performed to evaluate the global metabolic impact of these modifications and to identify additional engineering targets. Based on these insights, overexpression of acetyl-CoA carboxylase to enhance malonyl-CoA synthesis, pantothenate kinase to expand the CoA pool, and ATP citrate lyase to convert accumulated citrate into acetyl-CoA was implemented. These modifications significantly improved orsellinic acid production to 80 mg/L.

Furthermore, introduction of a plant-derived prenyltransferase enabled the conversion of orsellinic acid into grifolic acid (2.5 μg/g-DCW), achieving *de novo* biosynthesis of an orsellinic acid-derived meroterpenoid in *E. coli*. This study demonstrates that engineered *E. coli* is a promising microbial platform for the sustainable production of pharmacologically valuable orsellinic acid-derived meroterpenoids.