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Editorial

Biosynthesis of natural products from medicinal plants: Challenges, progress and prospects

Medicinal plants play a crucial role in traditional Chinese medicine and modern pharmaceuticals, serving as valuable resources for natural products used for plant-based medicines and new drugs. Nevertheless, the conventional techniques for acquiring natural products have been unable to meet the increasing requirements of drug research and development. Chemical synthesis of natural products are usually complex process and might bring the risk of causing environmental problems. The extraction of natural products from medicinal plants are difficult and impractical, resulting in inefficient outputs. The creative methods and strategies are imperative to be developed to enhance the production of natural product from medicinal plants. Therefore, focusing on the biosynthetic pathways, metabolic engineering, and synthetic biology of natural products provides the avenues for obtaining abundant natural product resources.

The Journal of *Chinese Herbal Medicines* (CHM) encourages authors to publish high-quality articles or reviews in the field of natural product biosynthesis. In the past decade, many papers published on CHM have been focused on the biosynthesis and metabolic engineering of natural products from medicinal plants (Xu et al., 2016, Wang et al., 2015, Wang et al., 2017, Zha & Zi, 2021). With the development of technologies, especially multi-omics and gene editing techniques (e.g., CRISPR-Cas9), significant progress has been made in elucidating the biosynthetic pathways and regulatory networks of natural products in medicinal plants. The review in the forthcoming issue of this journal titled “Strategies on biosynthesis and production of bioactive compounds in medicinal plants” (Guo et al., 2024) summarized the recent advancements in the research on the biosynthesis of natural product, including genetic engineering, plant cell culture engineering, metabolic engineering, and synthetic biology. Here, the challenges of increasing natural products from medicinal plants were outlined, and the progress of biosynthetic strategies was demonstrated. In addition, the prospects of biosynthesis of natural products from medicinal plants were also discussed.

1. Challenges in improving natural products in medicinal plants

The environmental conditions, the genetic variations in tissue culture, the complexity of metabolic engineering, along with the technological limitations, are the main challenges for improving the production of natural products in medicinal plants. Natural products are usually secondary metabolites produced in certain special parts of medicinal plants and often require years of accumulation to reach high content in plants. Generally, medicinal

plants grown in different geographical regions may contain different types and contents of their natural products due to the effect of climate and cultivation environments. To overcome the instability of medicinal plants, plant cell culture has been used widely to generate natural products. The biosynthetic pathways of natural products comprise many intermediate compounds and enzyme catalytic steps, especially those genes and enzymes with unknown function, which makes the designment and optimization of these pathways very complicated. The production of natural products with high yield and purity through biosynthesis still faces the significant challenges in elucidating those unpredictable enzymatic reactions and the substrate specificity of enzymes in these pathways. Besides, technological limitations also affect the efficiency of engineering metabolic pathways, such as the low efficiency of regulatory elements controlled the expression of exogenous genes. These challenges might be overcome through interdisciplinary research and the application of innovative technologies.

2. Progress in biosynthetic strategies of natural products

Over the past 20 years, the development of metabolic engineering, synthetic biology, multi-omics, and system biology have contributed greatly to increase the yields of natural products from medicinal plants. Nowadays, diverse strategies have been developed for engineering biosynthesis of natural products in microorganisms (Cravens et al., 2019). For example, the biosynthetic pathways of various natural products from medicinal plants have been successfully reconstructed in microbial systems (Abbasi et al., 2020). Modular synthesis is an efficient strategy for synthetic biology, which divides metabolic pathways into programmable modules for optimization to increase the production of certain natural products. Besides classical strains, a number of microorganisms have been developed as chassis cells for generation of natural products. Metabolic engineering based on genetic circuits and genome editing tools have been used to optimize the multi-step biosynthetic pathways. The strategy of biosensor-based high-throughput screening contributed to identify the transporters responsible for the secretion of natural products (Xu et al., 2020). Furthermore, the data generated from multi-omics and system biology provided more comprehensive understanding of the molecular mechanism related to the biosynthesis and regulation of natural products in plant cells. The integrated analysis of genomic, transcriptomic, proteomic, and metabolomic data provides more precise guidance for the designment and optimization of these metabolic pathways.

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3. Prospects for biosynthesis of natural products from medicinal plants

With the development of biology and sequencing technologies, many valuable natural products have been efficiently obtained from heterologous systems using metabolic engineering and synthetic biology techniques, such as artemisinin and paclitaxel. The herbal genomics provided abundant genetic resources for biosynthesis research of natural products (Chen and Song, 2016, Pei et al., 2023). Recently, the convenient and economical DNA synthesis enabled the enzymes to be synthesized on a large scale, which facilitates to construct and modify the biosynthetic pathways of natural products (Zheng et al., 2022). In particular, machine learning has been used as an effective alternative to elucidate the molecular mechanisms of complicated biosynthetic pathways. Compared with microbial chassis, plant chassis have significant advantages in enzyme structural modification and activity in the biosynthesis of natural products. The application of these innovative technologies is beneficial for the sustainable production of natural products, which will provide abundant chemical resources for pharmaceutical research and healthcare industry.

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