

Editorial

Synthesis of Natural Products Using Engineered Plants and Microorganisms

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Microorganisms and plants, particularly medicinal herbs, are abundant sources of diverse natural products, many of which are bioactive molecules with significant pharmaceutical or health benefits, and include artemisinin [1,2], ginsenosides [3], and *Ganoderic* triterpenes [4]. However, the contents of these bioactive compounds in their natural sources are often low [5]. The advancement of omics technologies and synthetic biology has opened new avenues for producing these valuable molecules through metabolically engineered plants and microorganisms [6]. Notable examples include the scaled-up production of artemisinin, rare ginsenosides, and various other natural products, which have potential applications in drugs, cosmetics, functional foods, animal feed, and other health-related products [7]. There is growing interest in utilizing cutting-edge synthetic biology technologies to further enhance the utilization of these natural products through the engineering of both plants and microorganisms [8].

This Special Issue is a collection of relevant research articles and reviews that highlight recent advancements in the production of bioactive natural products using engineered plants or microorganisms. Zhao, et al. summarized the artemisinin biosynthesis pathway, discussed advances in heterologous production using *Escherichia coli* and *Saccharomyces cerevisiae*, and explored metabolic engineering strategies in *Artemisia annua* and other plants to enhance artemisinin yields [9]. Zhang, et al. examined the pharmacological activities, biosynthesis pathways, extraction methods, and advances in the biotransformation and microbial synthesis of *Epimedium* flavonoids. Moreover, they discussed strategies to boost the industrial-scale production and utilization of *Epimedium* flavonoids [10]. Xu, et al. described the extraction, content determination, bioactivities, and product development of *Lycium ruthenicum* Murray's bioactive substances, and discussed their potential medicinal and economic value [11]. Drożdżyński, et al. explored how plants and their endophytes adapt to harsh environments, focusing on the bioactive metabolites produced by them in synanthropic ruderal plants for potential use in agriculture and medicine [12]. Su, et al., using transcriptome and metabolome tools, revealed that the adaptation of *Citrus reticulata* 'Chachi' to a saline environment enhanced its high production of naringin and narirutin [13].

The function of bioactive natural products in plants and microorganisms are discussed in this Special Issue. Ma, et al. investigated the triterpenoids and ergostane steroids in *Ganoderma luteomarginatum*, which is distributed in Hainan province, China, and their evaluation of several natural products indicated that certain natural products displayed potential anti-tumor effects [14]. Alanazi, et al. found that *Syzygium aromaticum* (clove) oil had the ability to inhibit methicillin-resistant *Staphylococcus aureus* infection [15]. Sun, et al. identified and evaluated the anti-inflammatory constituents in *Ardisia Japonica* Herba (AJH) extracts, and found that ethyl acetate extract (EA) displayed significant anti-inflammatory activity and contained key pharmacodynamic components like bergenin,



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quercetin, and epigallocatechingallate, crucial for treating acute lung injury (ALI) [16]. Zhang, et al. found that ginsenoside Rb1, compound K, and 20(S)-protopanaxadiol had the ability to attenuate high-fat-diet-induced hyperlipidemia in rats by modulating the gut microbiota and bile acid metabolism [17].

Sun, et al. successfully increased the yield of 1,4-diaminobutane to 272 mg/L from engineered *E. coli* via the optimization of the synthesis of the cofactors PLP and NADPH [18]. Caballero Cerbon, et al. highlighted that eliminating L-cysteine desulhydrases is key to improving L-cysteine production in engineered microbes, and outlined several strategies to tackle this issue [19]. Li, et al. demonstrated that biological nano selenium (SeNPs) and sodium selenite (Na_2SeO_3) treatments enhanced the organic selenium content in cowpea pods, and identified that a certain ABC transporter family played a crucial role in selenium absorption and transport [20]. Tu, et al. isolated *Klebsiella aerogenes* TL3 from termite guts, and demonstrated that it could degrade lignin anaerobically through a novel mechanism involving C-O and C-C bond cleavage, side chain oxidation, demethylation, and aromatic ring destruction [21].

Despite significant achievements in the synthesis of natural products using engineered plants and microorganisms, many bioactive natural products remain undeveloped [22]. Therefore, it is essential to leverage interdisciplinary tools, such as synthetic biology and engineering biology, to promote the development of related industries [23]. Through close collaboration between academia and industry, it is anticipated that a greater number of bioactive natural products could be discovered and utilized via engineered plants and microorganisms, thereby promoting technological innovation and market expansion in related industries.

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References

1. Ro, D.K.; Paradise, E.M.; Ouellet, M.; Fisher, K.J.; Newman, K.L.; Ndungu, J.M.; Ho, K.A.; Eachus, R.A.; Ham, T.S.; Kirby, J.; et al. Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature* **2006**, *440*, 940–943. [[CrossRef](#)] [[PubMed](#)]
2. Paddon, C.J.; Keasling, J.D. Semi-synthetic artemisinin: A model for the use of synthetic biology in pharmaceutical development. *Nat. Rev. Microbiol.* **2014**, *12*, 355–367. [[CrossRef](#)] [[PubMed](#)]
3. Yan, X.; Fan, Y.; Wei, W.; Wang, P.; Liu, Q.; Wei, Y.; Zhang, L.; Zhao, G.; Yue, J.; Zhou, Z. Production of bioactive ginsenoside compound K in metabolically engineered yeast. *Cell Res.* **2014**, *24*, 770–773. [[CrossRef](#)] [[PubMed](#)]
4. Yuan, W.; Jiang, C.; Wang, Q.; Fang, Y.; Wang, J.; Wang, M.; Xiao, H. Biosynthesis of mushroom-derived type II ganoderic acids by engineered yeast. *Nat. Commun.* **2022**, *13*, 7740. [[CrossRef](#)]
5. Zhang, X.; Miao, Q.; Pan, C.; Yin, J.; Wang, L.; Qu, L.; Yin, Y.; Wei, Y. Research advances in probiotic fermentation of Chinese herbal medicines. *Imeta* **2023**, *2*, e93. [[CrossRef](#)]
6. Choi, K.R.; Jang, W.D.; Yang, D.; Cho, J.S.; Park, D.; Lee, S.Y. Systems Metabolic Engineering Strategies: Integrating Systems and Synthetic Biology with Metabolic Engineering. *Trends Biotechnol.* **2019**, *37*, 817–837. [[CrossRef](#)]
7. Ma, J.; Gu, Y.; Marsafari, M.; Xu, P. Synthetic biology, systems biology, and metabolic engineering of *Yarrowia lipolytica* toward a sustainable biorefinery platform. *J. Ind. Microbiol. Biotechnol.* **2020**, *47*, 845–862. [[CrossRef](#)]
8. Chen, R.; Gao, J.; Yu, W.; Chen, X.; Zhai, X.; Chen, Y.; Zhang, L.; Zhou, Y.J. Engineering cofactor supply and recycling to drive phenolic acid biosynthesis in yeast. *Nat. Chem. Biol.* **2022**, *18*, 520–529. [[CrossRef](#)] [[PubMed](#)]
9. Zhao, L.; Zhu, Y.; Jia, H.; Han, Y.; Zheng, X.; Wang, M.; Feng, W. From Plant to Yeast—Advances in Biosynthesis of Artemisinin. *Molecules* **2022**, *27*, 6888. [[CrossRef](#)]
10. Zhang, X.; Tang, B.; Wen, S.; Wang, Y.; Pan, C.; Qu, L.; Yin, Y.; Wei, Y. Advancements in the Biotransformation and Biosynthesis of the Primary Active Flavonoids Derived from Epimedium. *Molecules* **2023**, *28*, 7173. [[CrossRef](#)]

11. Xu, M.-L.; He, Y.-F.; Xie, L.; Qu, L.-B.; Xu, G.-R.; Cui, C.-X. Research Progress on Active Ingredients and Product Development of *Lycium ruthenicum* Murray. *Molecules* **2024**, *29*, 2269. [[CrossRef](#)]
12. Drożdżyński, P.; Rutkowska, N.; Rodziejewicz, M.; Marchut-Mikołajczyk, O. Bioactive Compounds Produced by Endophytic Bacteria and Their Plant Hosts—An Insight into the World of Chosen Herbaceous Ruderal Plants in Central Europe. *Molecules* **2024**, *29*, 4456. [[CrossRef](#)] [[PubMed](#)]
13. Su, J.; Peng, T.; Bai, M.; Bai, H.; Li, H.; Pan, H.; He, H.; Liu, H.; Wu, H. Transcriptome and Metabolome Analyses Provide Insights into the Flavonoid Accumulation in Peels of Citrus reticulata ‘Chachi’. *Molecules* **2022**, *27*, 6476. [[CrossRef](#)] [[PubMed](#)]
14. Ma, Q.; Zhang, S.; Yang, L.; Xie, Q.; Dai, H.; Yu, Z.; Zhao, Y. Lanostane Triterpenoids and Ergostane Steroids from Ganoderma luteomarginatum and Their Cytotoxicity. *Molecules* **2022**, *27*, 6989. [[CrossRef](#)] [[PubMed](#)]
15. Alanazi, A.K.; Alqasbi, M.H.; Alrouji, M.; Kuriri, F.A.; Almuhan, Y.; Joseph, B.; Asad, M. Antibacterial Activity of Syzygium aromaticum (Clove) Bud Oil and Its Interaction with Imipenem in Controlling Wound Infections in Rats Caused by Methicillin-Resistant Staphylococcus aureus. *Molecules* **2022**, *27*, 8551. [[CrossRef](#)]
16. Sun, S.; Liu, X.; Zhao, D.; Zheng, L.; Han, X.; Tian, Y.; Feng, S. Discovery of the Active Compounds of the Ethyl Acetate Extract Site of Ardisia japonica (Thunb.) Blume for the Treatment of Acute Lung Injury. *Molecules* **2024**, *29*, 770. [[CrossRef](#)]
17. Zhang, K.-X.; Zhu, Y.; Song, S.-X.; Bu, Q.-Y.; You, X.-Y.; Zou, H.; Zhao, G.-P. Ginsenoside Rb1, Compound K and 20(S)-Protopanaxadiol Attenuate High-Fat Diet-Induced Hyperlipidemia in Rats via Modulation of Gut Microbiota and Bile Acid Metabolism. *Molecules* **2024**, *29*, 1108. [[CrossRef](#)]
18. Sun, T.; Zhao, Y.; Wang, J.; Kang, W.; Sun, X.; Sun, Y.; Chu, M.; Liu, Z.; Lu, F.; Li, M. Increasing 1,4-Diaminobutane Production in Escherichia coli by Optimization of Cofactor PLP and NADPH Synthesis. *Molecules* **2024**, *29*, 3094. [[CrossRef](#)]
19. Caballero Cerbon, D.A.; Gebhard, L.; Dokuyucu, R.; Ertl, T.; Härtl, S.; Mazhar, A.; Weuster-Botz, D. Challenges and Advances in the Bioproduction of L-Cysteine. *Molecules* **2024**, *29*, 486. [[CrossRef](#)]
20. Li, L.; Xiong, Y.; Wang, Y.; Wu, S.; Xiao, C.; Wang, S.; Cheng, S.; Cheng, H. Effect of Nano-Selenium on Nutritional Quality of Cowpea and Response of ABCG Transporter Family. *Molecules* **2023**, *28*, 1398. [[CrossRef](#)]
21. Tu, Z.; Geng, A.; Xiang, Y.; Zayas-Garriga, A.; Guo, H.; Zhu, D.; Xie, R.; Sun, J. Lignin Degradation by Klebsiella aerogenes TL3 under Anaerobic Conditions. *Molecules* **2024**, *29*, 2177. [[CrossRef](#)] [[PubMed](#)]
22. Bureau, J.A.; Oliva, M.E.; Dong, Y.; Ignea, C. Engineering yeast for the production of plant terpenoids using synthetic biology approaches. *Nat. Prod. Rep.* **2023**, *40*, 1822–1848. [[CrossRef](#)] [[PubMed](#)]
23. Brooks, S.M.; Alper, H.S. Applications, challenges, and needs for employing synthetic biology beyond the lab. *Nat. Commun.* **2021**, *12*, 1390. [[CrossRef](#)] [[PubMed](#)]

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