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Synthetic biomanufacturing of plant natural products: technological breakthroughs and industrial transformation

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Abstract. Plant natural products possess significant application value in medicine, food, and agriculture owing to their diverse biological activities. However, traditional production methods relying on plant extraction face challenges including resource scarcity, low efficiency, and environmental pressures. Synthetic biology provides innovative strategies for efficient biosynthesis of plant natural products through the analysis of metabolic pathways, the mining of key enzymes, the optimization of chassis cells, and the reconstruction of metabolic networks. Herein, we systematically review core technological advances in synthetic biology for plant natural product production, including:multi-omics-driven elucidation of metabolic pathways, enzyme optimization through protein engineering and directed evolution, adaptive modification of chassis cells (e.g., Saccharomyces cerevisiae and Escherichia coli), and integration of artificial intelligence and automation technologies. We discuss the industrial potential of synthetic biology in medicine, food, and environmental protection through representative cases (e.g., breviscapine, ginsenosides, and tanshinones). Despite persistent challenges such as metabolic pathway complexity, insufficient enzyme catalytic efficiency, and high industrialization costs, synthetic biology—through interdisciplinary integration and policy support—is poised to enable green, sustainable production of plant natural products.

Keywords: synthetic biology, plant natural products, metabolic pathways, chassis cells, artificial intelligence

1. Introduction

Plant natural products are a class of small molecular compounds with diverse structures and significant biological activities produced by plant secondary metabolism, including terpenoids, alkaloids, phenylpropanoids, and other active ingredients. Plant natural products have irreplaceable roles in drug development, functional foods, and green pesticides. However, the traditional production methods of plant extraction are limited by resource shortages, long plant growth cycles, low extraction efficiency, and heavy pollution from chemical synthesis, which makes it difficult to meet the growing market demand.

Synthetic biology, an interdisciplinary field integrating biology, engineering, and informatics, offers a novel approach to efficiently manufacture plant-derived natural products using microbial cell factories through rational design. In recent years, propelled by breakthroughs in metabolomics, gene editing, and computational biology, synthetic biology has witnessed significant advancements in metabolic pathway engineering, enzyme function optimization, and chassis cell development. For instance, the heterologous synthesis of artemisinin in microorganisms has been successfully translated into industrial production, substantially reducing the costs of antimalarial medications. Moreover, the synthetic pathway for paclitaxel precursors in yeast has been continuously refined, presenting a sustainable alternative for anticancer drug production.

In this review, we systematically summarize the key technological systems of synthetic biology employed in the production of plant natural products. By integrating typical application cases, we delve into aspects such as metabolic pathway analysis, key enzyme discovery, chassis cell modification, and synthesis optimization strategies. Additionally, through in-depth analyses of representative examples, including brecaperon, ginsenoside, and tanshinone, we identify the current technical bottlenecks and hurdles impeding industrialization. Furthermore, we explore the emerging trend of integrating artificial intelligence and automation technology with synthetic biology, and discuss its potential in advancing green biological production. This comprehensive overview aims to offer theoretical guidance for research endeavors and industrial transformations in related fields.

2. Technical system: from multi-omics mining to production system optimization

2.1. Metabolic pathway analysis

The biosynthesis of plant natural products usually involves complex reaction networks catalyzed by multiple enzymes. Understanding these complex metabolic pathways is the cornerstone for the production of plant natural products through synthetic biology. In recent years, remarkable progress has been made in analyzing the metabolic pathways of active ingredients, such as terpenoids, alkaloids, and phenylpropanoids. Multi-omics technology plays an indispensable role in this process.

Genomics can analyze the genetic background of an organism at the molecular level and provide a basic framework for metabolic pathways. Yan's team [1] established a multi-gene efficient screening technology based on the analysis of the taxane molecular structure and taxane biosynthesis-related gene family, and discovered the key gene tot1 for taxol biosynthesis. They mapped the chromosome-level genome map of Taxus chinensis var. chinensis, which laid the genetic foundation for taxol pathway analysis. Through this analysis, the researchers identified a number of genes closely related to paclitaxel synthesis, providing key information for the subsequent in-depth study of the paclitaxel biosynthesis pathway. Transcriptomics focuses on the transcription level of genes in specific tissues or conditions, reflects real-time gene expression, and helps to target key genes. Song's team [2] identified multiple floral organ regulatory genes in Dendrobium officinale through the combined analysis of DAP-seq and RNA-seq, and verified the interaction between DoAP3-3 and MADS6, which influenced floral development. This provided a reference for the functional study of transcription factors. Metabolomics focuses on the quantitative and differential analysis of metabolites. Jiang et al. [3] used UPLC-MS to find significant differences in the metabolic profiles of filature flower fruits of different genotypes and identified a total of 723 metabolites. Comparative analyses showed that each genotype had some characteristic metabolites, and flavonoids, triterpenoids, and phenolic acids were significantly associated with the antioxidant capacity of fruit extracts. Compared with other genotypes, genotypes Rr-7 and Rr-f have greater potential for medicinal and functional food applications. This finding provides useful information for the development of new genotype-based functional foods and also for determining the optimal genotype for plant breeding.

Multi-omics technologies complement each other at different levels and offer powerful technical means for in-depth analysis of plant natural product metabolic pathways. Future research on plant natural product metabolic pathways should further integrate computational biology and high-throughput screening techniques to overcome the bottlenecks in pathway module compatibility and enzyme catalytic efficiency, thereby promoting the green biomanufacturing of plant natural products.

2.2. Key enzyme mining

In the synthetic pathways of plant natural products, key enzymes catalyze specific chemical reactions. These reactions influence the direction of metabolic pathways, the formation of products, and ultimately determine the structure and yield of the products. The efficient discovery and engineering of key enzymes within product synthesis pathways represent one of the crucial steps in synthetic biology.

Coping with salt and alkali stress is a major challenge during plant growth. By exploring key enzymes and their coding genes associated with salt and alkali tolerance, researchers can gain a deep understanding of the molecular mechanisms underlying plant salt and alkali tolerance. This understanding provides a theoretical basis and genetic resources for breeding salt- and alkali-tolerant plant varieties. Through transcriptome analysis of salt-tolerant soybeans, a salt-induced inositol polyphosphate-5-phosphatase gene (Gs5PTase8) was identified. Gs5PTase8 is closely linked to plant salt and alkali tolerance and is widely present in eukaryotes. Functional characterization revealed that GS5Ptase8 is an important phosphatase regulating the reverse reaction. To biochemically characterize the substrate properties of Gs5PTase8, the team led by Lin from Sichuan University [4] used Arabidopsis thaliana precursor PIP3 gene (prePIP3) overexpression and knockout mutants to identify a novel ligand-receptor signaling cascade (PIP3-RLK7-MPK3/6). This discovery provides a new molecular mechanism for understanding plant responses to salt stress and potential targets for breeding salt-tolerant crops, thus helping to address the threat of global soil salinization to agricultural production. Plant cytochrome P450 enzymes play a crucial role in diversifying and modifying the functions of plant natural products. Chen et al. [5] increased the supply of precursors and supplemented key amino acid genes to construct 11,20-dihydroxyrusts. They also created a microenvironment conducive to P450 expression by enhancing the supply of cofactor NADPH, expanding the endoplasmic reticulum, promoting heme synthesis, and regulating iron ions, thereby achieving the efficient production of 11,20-dihydroxyrusts.

The discovery and in-depth study of key enzymes are of great value for understanding the mechanisms of plant stress resistance and enhancing the production of plant natural products. This knowledge will facilitate the advancement of agricultural production and the synthesis of plant natural products. In the future, enzyme engineering will progress towards directed evolution, rational design, and AI-assisted screening, aiming to achieve multi-objective functional optimization, including high activity, thermotolerance, and stress tolerance.

2.3. Chassis cells

Chassis cells serve as the host cells for constructing cell factories in synthetic biology. Selecting appropriate chassis cells is vital for the efficient synthesis of plant natural products. Currently, Saccharomyces cerevisiae and Escherichia coli are the commonly used chassis cells.

Saccharomyces cerevisiae, a eukaryotic microorganism, features a complete intracellular membrane system and has evolved various organelles, including mitochondria, peroxisomes, the Golgi apparatus, the endoplasmic reticulum, lipid droplets, and vacuoles [6]. It offers advantages such as a well-characterized genetic background, ease of genetic manipulation, rapid growth, and a mature fermentation process. The methods for introducing foreign genes into Saccharomyces cerevisiae mainly include homologous recombination replacement, the Cre-lox P system, the serine integrase system, nuclease-based approaches like the Zinc Finger Nuclease (ZFN), the Transcription Activator-Like Effector Nuclease (TALEN), and the CRISPR-Cas system [7]. Zhang et al. [8] developed a gene autonomous oscillatory silencing strategy. By integrating global metabolic flow simulation, combining metabolic flux analysis (FBA) and the optimized knock-out (OptKnock) algorithms with the Saccharomyces cerevisiae Genome Metabolic Model (GEM), they applied this strategy to oleanolic acid production. The oleanolic acid yield of the engineered strain r_3a was over five times higher than that of the original strain OA07. On the fourth day of high-density fermentation, the oleanolic acid yield of the modified strain R_3A reached 1232.19±36.75 mg/L, representing a 184% increase compared to the previously reported highest yield. Currently, Saccharomyces cerevisiae has been successfully used to synthesize various plant natural products, such as tanshinones and paclitaxel precursors. Wang's team [9] engineered Saccharomyces cerevisiae for chrysin synthesis. They introduced the gene F6H encoding flavonoid 6-hydroxylase and the gene ATR2 encoding cytochrome P450 reductase 2 into the chassis strain, successfully constructing the baicalein synthesis pathway.

Escherichia coli, a prokaryotic organism, exhibits characteristics such as rapid growth, low cultivation cost, and straightforward genetic manipulation. Its relatively small genome facilitates gene editing and modification. Commonly, E. coli is utilized to express simple enzymes or metabolic pathway modules involved in the synthesis of plant natural products. To synthesize certain plant natural products or their precursors, genes related to plant natural product synthesis are introduced into E. coli to generate recombinant strains. Luo's team [10] employed metabolic engineering to modify Escherichia coli for gallic acid production. By leveraging plasmid copy number and promoter engineering, they constructed an optimized pathway within the chassis strain. In combination with protein engineering, they obtained the rate-limiting enzyme mutant PobAM2/A45S/V47P, enabling the gallic acid production level to reach 3.6 g/L in shake flask cultures. Subsequently, the strain stability and fermentation conditions were optimized in a 5-L fermenter, resulting in a gallic acid yield of 26.7 g/L and a sugar-acid conversion rate of 0.15 g/g. However, due to the absence of a eukaryotic protein post-translational modification system in Escherichia coli, for some key enzymes in plant natural product synthesis that require complex modifications, it may be challenging to obtain active proteins when expressed in this bacterium.

2.4. System integration and production optimization

2.4.1. Path module coordination and dynamic regulation

The synthesis of plant natural products often involves multiple metabolic pathway modules. The coordinated expression and dynamic regulation among these modules are crucial for enhancing the yield and quality of products. In synthetic biology, sensing promoters and feedback regulatory loops serve as the core elements for achieving the coordination and dynamic regulation of pathway modules.

Sensing promoters can rapidly respond to changes in external environmental signals, such as temperature, pH, and the concentration of specific chemicals, thereby enabling precise regulation of gene expression. He's team [11] isolated Pseudomonas PA1201 from the rhizosphere of rice in the suburbs of Chongqing. Its metabolite, phenazine 1-amide, can inhibit plant pathogens. However, the original strain had a fermentation titer of only 0.08 g/L, and its optimal fermentation temperature was 28°C, which limited its industrialization. The team identified PrhlI, a highly efficient temperature-sensitive expression promoter regulated by quorum sensing. This promoter exhibited 2.2-fold higher activity at 37°C compared to 28°C. The engineered strain UP46 achieved a fermentation titer of 14.1 g/L at 37°C, representing a 180-fold increase. Moreover, the yield remained stable in a 100-liter fermenter.

Feedback inhibition is prevalent in the synthesis of numerous plant natural products, where the accumulation of products inhibits the activities of key enzymes in the synthesis pathway once it reaches a certain level. Huang's team [12] discovered that in cotton, the VQ protein JAVL and the MYC2-like transcription factor GoPGF form a negative feedback regulatory loop. GoPGF can directly activate the transcription of JAVL, while JAVL suppresses the transcription of GoPGF. These two components maintain a stable expression equilibrium, thereby regulating the size of cotton pigment glands and the content of secondary metabolites. Under normal conditions, the ratio of GoPGF to JAVL (G/J) is maintained at approximately 0.8-1.2 at the mRNA level. However, when cotton is infested by insects, this ratio rapidly increases to 2.5-3.0 at the mRNA level, with a corresponding increase at the protein level. Therefore, the rational utilization of sensing promoters and feedback regulatory loops can precisely regulate metabolic pathways, enhance the synthesis efficiency of plant natural products, and facilitate industrial development.

2.4.2. Production process optimization

The production process encompasses multiple key stages, including cell culture, regulation of fermentation conditions, and product isolation and purification. These stages play a decisive role in determining the yield and quality of plant natural products. Optimizing the production process can remarkably enhance the production efficiency of cell factories and boost the yield of target plant natural products.

During cell culture, cell proliferation and viability are commonly analyzed using detection methods such as cell counting, fluorescence staining, and enzyme-linked immunosorbent assay. These traditional methods are time-consuming and labor-intensive, failing to meet the requirements of high-throughput detection. Moreover, they are destructive detection techniques, which can impact subsequent experimental research. In recent years, a microfluidic impedance sensor capable of real-time cell state monitoring has been developed by integrating microfluidic technology with cellular impedance sensors [13]. Its working principle involves applying a sinusoidal voltage at a specific frequency and measuring the changes in capacitance and resistance between the cell and the electrode using alternating current to study the cell's physiological responses. For instance, after cell seeding, cells gradually adhere to the electrode layer. The insulating properties of cells can alter the local environment at the cell-electrode interface. As more cells attach to the electrode surface, the flow of current through the cells is impeded, causing the impedance to increase gradually. Conversely, when toxic drugs are present in the environment, cells undergo apoptosis or detach from the electrode surface, leading to a gradual decrease in impedance. This technology enables the study of cellular life activities such as growth, proliferation, and migration and can also be utilized for drug screening.

During the process of product separation and purification, traditional separation techniques, such as solvent extraction and column chromatography, also encounter certain challenges. Solvent extraction typically necessitates the use of a substantial amount of organic solvents. This not only incurs high costs but also readily leads to environmental pollution. Additionally, it may cause the loss or denaturation of the target product during the extraction process. Although column chromatography offers an effective separation outcome, its complex operation and long processing cycle render it challenging to achieve large-scale continuous production. The emerging aqueous two-phase extraction technology presents a novel solution for product separation and purification. Aqueous two-phase extraction exploits a two-phase system formed by two immiscible hydrophilic polymers or by polymers and inorganic salts in an aqueous solution. The separation of the target product is accomplished based on the differences in partition coefficients between the two phases. For instance, Hu et al. [14] demonstrated through optimization experiments that under the conditions of a 26.07% ethanol-24.81% ammonium sulfate aqueous two-phase system and 10.28 minutes of sonication, the extraction rate of Schisandrin A could reach 98.48% and the partition coefficient was 43.80. This technology features mild operating conditions, ease of scale-up, and continuous operation capabilities. It can effectively circumvent the issues associated with traditional methods, enhance the purity and yield of products, and provide robust support for the industrial production of plant natural products.

2.4.3. Modification of biological components

Synthetic biological parts consist of regulatory elements (such as promoters, terminators, and ribosomal binding sites) that govern gene expression, and structural elements (genes encoding specific catalytic enzymes in the synthetic pathway) that execute specific functions. Clearly characterized and standardized biological components serve as the foundation for the engineering development of synthetic biological systems.

Currently, the machine-learning-based function prediction of biological components has emerged as a focal point of interdisciplinary research, yielding a series of innovative scientific outcomes. Zhang et al. [15] recently proposed a deep-learning framework named Deep ICSH. By integrating multi-level sequence features, transcriptional features, and epigenetic features, and employing the CNN algorithm to capture combinations of biological signals closely associated with silencers, Deep ICSH can effectively identify cell-specific silencers within the human genome. Leveraging the MRL [16] and half-life [17] datasets, Wang's team at Tsinghua University has achieved a breakthrough in the analysis of mRNA sequence functions [18]. Using the self-developed Neuron Motif tool, the researchers constructed a comprehensive, customized pipeline for modeling the relationship between RNA sequences and their functions. This pipeline, which encompasses three core steps—motif discovery, motif contribution assessment, and motif interaction analysis—can not only accurately identify key cis-acting RNA motifs in mRNA but also elucidate the intricate interactions among them. Barissi et al. [19] proposed a machine-learning approach based on physical descriptors. By utilizing the physical properties of DNA, such as the electrostatic mode of bases, hydrogen bonds, and hydrophobicity, obtained through molecular dynamics simulations as input, they accurately predicted the binding affinity between transcription factors and DNA (TFs-DNA) determined by various experimental techniques. This method significantly outperforms traditional approaches based on Position Weight Matrices (PWM) and sequence feature analysis.

Through the accurate prediction and in-depth analysis of biological component functions, researchers can design and modify these components more targetedly. This approach enables the optimization of synthetic biological systems, accelerates the development of synthetic biology in the production of plant natural products, and provides robust support for achieving efficient and sustainable biofabrication.

In summary, the core technologies of synthetic biology in the production of plant natural products, ranging from the elucidation of metabolic pathways, to the discovery of key enzymes, the selection and modification of chassis cells, and the optimization of

the synthesis process, constitute an organic whole. These technologies are interconnected and mutually reinforcing. Their continuous development and improvement have laid a solid foundation for the efficient biosynthesis of plant natural products, as illustrated in Figure 1:

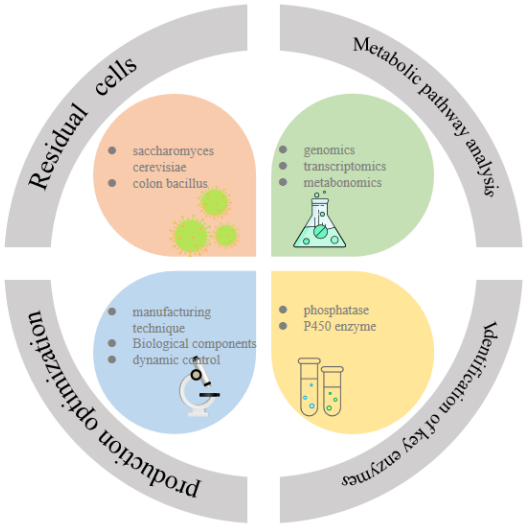

Figure 1. A comprehensive overview of the core technologies of synthetic biology in the production of plant natural products

3. Production and application: from experimental platform to industrial practice

3.1. Medical field

In the pharmaceutical field, plant natural products serve as important sources of drugs and their lead compounds. Among the drugs approved over the past 40 years, natural products and their derivatives account for one-quarter. Currently, the production of plant natural products predominantly relies on traditional plant extraction methods, which are unable to meet the demands of social development. Moreover, some medicinal plant species are endangered, and these plants are either difficult to cultivate artificially, have a long growth cycle, or contain low levels of active ingredients. The extraction process is cumbersome, and the yield is low, making it challenging to achieve environmentally friendly large-scale production [20-22]. This section will focus on the application of synthetic biology to breviscapine, ginsenosides, and tanshinones, aiming to address the aforementioned production challenges.

Breviscapine is the active ingredient of the traditional Chinese medicine Erigeron breviscapus. It exhibits effects such as vasodilation and promotion of blood circulation, and is widely applied in the clinical treatment of cardiovascular and cerebrovascular diseases [23]. Currently, the heterologous synthesis pathway of breviscapine has been elucidated: flavonoid synthase II catalyzes naringin to form apigenin, which is then processed by Flavonoid 6-Hydroxylase (F6H) and Flavonoid 7-O-Glucuronic Acid Transferase (F7GAT) to produce breviscapine. Liu et al. [24] introduced the heterologous synthesis pathway of breviscapine into Saccharomyces cerevisiae to construct an engineered strain for breviscapine production. Subsequently, they regulated the genes related to the metabolic pathway and optimized the fermentation conditions. Eventually, the production of breviscapine in the fermenter reached 108 $mg \cdot L^{-1}$. Moreover, Wang et al. [25] introduced the heterologous synthesis pathway of breviscapine into Yarrowia lipolytica as the chassis cell. Through metabolic strategies including key gene screening, isoenzyme screening, and metabolic pathway optimization, they successfully constructed an engineered strain of Yarrowia lipolytica with high-yield breviscapine production. The yield of breviscapine increased by 80%, which was three times that of Saccharomyces cerevisiae.

Ginsenosides are the main active components of Panax ginseng. They exhibit a wide range of pharmacological activities and have significant effects on regulating immunity, relieving fatigue, anti-inflammation, anti-oxidation, anti-tumor, and hypoglycemic functions. Ginsenosides are highly sought-after as medicines and health products, with a substantial market demand. However, ginseng resources are scarce, the growth cycle is long (5-7 years), artificial cultivation faces continuous cropping obstacles, and the content of ginsenosides in ginseng is low [26]. Consequently, its supply is far from meeting people's needs. The team led by Zhang from the Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, and the team led by Guoping Zhao from the Center for Excellence in Molecular Plant Science, Chinese Academy of Sciences, have both achieved remarkable results in the biosynthesis of ginsenosides. Zhang's research team optimized the mevalonate pathway, refined the combination of gene modules, regulated the expression of the gene encoding damalenediol II (an important intermediate in the ginsenoside biosynthesis pathway) synthase and the ERG7 gene in the ergosterol synthesis pathway, and optimized the fermentation process. They created an efficient yeast cell factory with a yield of 15 g/L of damalenediol II [27] and analyzed the biosynthetic pathway of damalane

saponins [28]. The team also significantly enhanced the synthesis efficiency of protopanaxadiol by constructing a new reaction compartment. On this basis, they introduced an efficient synthesis module for ginsenoside CK and obtained an engineered strain that could produce 5 g/L of ginsenoside CK in a 5 L fermenter [29].

Tanshinones are abietane diterpenoids derived from the traditional Chinese medicine Salvia miltiorrhiza, mainly present in the rhizome of this plant. Tanshinone is a general term for compounds such as tanshinone IIA, tanshinone IIB, tanshinone I, and cryptotanshinone. Currently, tanshinones are mainly used in the treatment of cardiovascular diseases. Additionally, they exhibit antibacterial, anti-inflammatory, anti-oxidative, anti-tumor, and anti-myocardial hypoxia pharmacological activities [30, 31]. Currently, tanshinones are primarily extracted from Salvia miltiorrhiza. However, the long growth cycle of this plant and the complex extraction steps of tanshinones have hindered its further development [32]. Members of the CYP72A subfamily in higher plants show certain conservation in their physiological functions [33]. Previous studies have indicated that the CYP450 gene is involved in the oxidation of GGPP to gibberellic acid, and rice OsCYP72A20 can regulate rice panicle germination [34]. Gibberellins, which are tetracyclic diterpenoids sharing the substrate GGPP with tanshinones, may represent a competitive pathway for tanshinone biosynthesis [35]. Nevertheless, the specific substrates of SmCYP72A395 and the biosynthetic pathways of secondary metabolites in Salvia miltiorrhiza are still under further investigation. The specific functions of SmCYP72A395 in regulating the biosynthesis of secondary metabolites in Salvia miltiorrhiza will be elucidated through in vitro enzymatic reactions and CRISPR-Cas9 technology. This will lay the foundation for analyzing the molecular mechanism underlying the complex biosynthesis of tanshinones.

Plant natural products are crucial sources of drugs and lead compounds in the medical field. However, traditional extraction methods suffer from numerous limitations. Synthetic biology provides solutions to these issues. For instance, in the synthesis of breviscapine, ginsenosides, and tanshinones, researchers have significantly increased product yields by constructing engineered bacteria, optimizing metabolic pathways, and refining fermentation conditions. Despite the remarkable progress of synthetic biology in the production of plant natural products, certain medicinal plants still encounter resource-related and extraction-related challenges. Additionally, technical and cost-related hurdles remain to be overcome.

3.2. Food field

Synthetic biology also finds extensive applications in food, agriculture, and environmental protection. In the food industry, its applications can be categorized into two types: the production of main food components (such as proteins, carbohydrates, and fats) and auxiliary food components (including amino acids, vitamins, and color and flavor compounds). Employing cell factories for food synthesis enhances land use efficiency, conserves water resources, and reduces the reliance on pesticides and fertilizers. Moreover, the food manufacturing processes enabled by synthetic biology are less susceptible to the natural environment. This characteristic allows for easier control of food quality standards, an improvement in the nutritional content of food, and the conferral of novel functions to food products. Synthetic biology has been widely utilized in the biosynthesis of functional foods, such as carotenoids, vitamin K2 (menaquinone-7), and human milk oligosaccharides [36]. Regarding fermented foods, synthetic biology can replicate traditional fermented food production by creating semi-synthetic microbial communities while precisely regulating the fermentation process to make the foods healthier. Notably, in 2021, Ma's research group [37] successfully harnessed synthetic biology technology to synthesize "artificial starch" using carbon dioxide as the raw material, achieving a groundbreaking "from 0 to 1" milestone.

3.3. Agricultural field

In the agricultural field, certain plant natural products possess insecticidal and antibacterial properties, which can be exploited to develop green pesticides. This approach helps reduce the application of chemical pesticides and mitigates environmental pollution. For instance, pyrethrin [38], a natural insecticide derived from Chrysanthemum cinerariifolium, exhibits advantages such as high efficacy, low toxicity, and easy degradation against pests. Employing synthetic biology techniques, researchers have endeavored to synthesize pyrethrins in microbial chassis cells. Through the analysis of the pyrethrin biosynthetic pathway, they introduced relevant key enzyme genes into chassis cells like Escherichia coli and Saccharomyces cerevisiae, thereby achieving the synthesis of pyrethrin precursors. Furthermore, some plant natural products have bioremediation capabilities, enabling them to degrade environmental pollutants. For example, Indian mustard produces phytochelate peptides, a unique type of plant natural product that plays a crucial role in remediating Cd-contaminated soils. Phytochelate peptides bind to cadmium ions, forming stable complexes that immobilize the cadmium ions within plant cells. This process reduces the toxicity of cadmium ions to plants and decreases the cadmium content in the soil, thus facilitating the bioremediation of Cd-contaminated soil. To a certain extent, the remediation efficiency can reach 30%-40% [39]. By leveraging synthetic biology technology, microbial cell factories capable of efficiently synthesizing these plant natural products can be constructed for environmental pollution control.

Synthetic biology has been applied widely, yielding remarkable results. It boosts plant natural product production in pharmaceuticals, and demonstrates unique value in food, agriculture, and environmental protection. These applications are crucial for promoting sustainable industry development, as shown in Table 1:

Table 1. A comparison table of the applications and roles of synthetic biology in various fields

Field	Products	Status quo	Synthetic Biology Applications	References
Field of medicine	Breviscapine	chemical synthesis is poor	Wang's team used Yersinia lipolytica, which was selected and optimized to increase the yield by 80%	[24, 25]
	Ginsenosides	Few resources and low content	Zhang's team created a yeast cell factory and reconstructed the reaction compartment to enhance the production of protoginsenediol and ginsenoside CK	[27, 28]
	tanshinone	Extraction is difficult	The Du Q team explored the function of SmCYP72A395 to lay the foundation for parsing the synthetic pathway	[35]
Field of food	Fermented food	Production control is difficult	Zhou et al. improved the health value of food by recreating fermentation process by creating semi-synthetic microbial communities	[36]
	Carotenoids and so on	Poor stability and high production cost	Liu et al. used cell factories to enhance resource utilization, stabilize quality, improve nutrition, and endow new functions	[36]
	Production of food	Low resource utilization	Ma and his research team have successfully used synthetic biology technology to synthesize "artificial starch" from carbon dioxide.	[37]
Field of agriculture	Pyrethroids	Pollution of the environment	Wang et al. dissect the pyrethrin biosynthetic pathway to achieve precursor synthesis	[38]
	Chelating peptide of plants	Cadmium pollution is serious	Microbial cell factories were constructed to synthesize plant chelating peptides for the treatment of cadmium contaminated soil	[39]

4. Challenges and prospects

As an interdisciplinary frontier technology, synthetic biology has brought revolutionary changes to the research and production of plant natural products. By leveraging a series of technological approaches, including metabolic pathway analysis, key enzyme discovery, chassis cell selection and engineering, and metabolic network optimization, significant achievements have been made in the synthesis of diverse plant natural products. These have demonstrated great application potential in the fields of medicine, food, agriculture, and environmental protection. However, the current development of synthetic biology in the domain of plant natural products still faces numerous challenges, such as the arduous reconstruction of complex metabolic pathways, inadequate optimization of enzyme functions, high costs of industrialization, and imperfect regulatory frameworks [40].

The key enzymes in plant natural product synthesis pathways often exhibit complex catalytic mechanisms and substrate specificity. Exogenous enzymes expressed in chassis cells may encounter issues such as low activity, poor stability, and low substrate affinity. A crucial problem to be addressed is how to rationally design and modify these enzymes and optimize their functions to adapt to the environment of chassis cells using technologies like protein engineering and directed evolution. Sun's team [41] constructed a D-oxalose-specific biosensor and obtained a mutant of D-oxalose-3-isomerase (CcDAE) derived from Clostridium cellulolyticum H10, which showed a 26.21% higher specific activity. This study not only successfully demonstrated that transcription factor-based biosensors possess significant application value in the directed evolution of proteases but also offered new insights for the modification of DAE enzymes. Ma's team [42] created a tannase mutant (mLptan1) through error-prone PCR. The mutant had an optimal reaction temperature increased by 5℃ and could achieve an 85% degradation rate of ester catechin in tea soup.

With the rapid advancement of technology and the increasing integration of interdisciplinary fields, the in-depth collaboration between synthetic biology and other frontiers such as artificial intelligence, big data, and nanotechnology is propelling the research on plant natural products to new heights. The robust data analysis, pattern recognition, and predictive capabilities of artificial intelligence will significantly facilitate the intelligent design of metabolic pathways, the precise optimization of enzyme functions, and the efficient adaptation of chassis cells. This will help overcome current bottlenecks in reconstructing complex pathways, enhancing enzyme catalytic efficiency, and controlling industrialization costs. Currently, the industry is in a golden development period characterized by the convergence of "policy dividend release, technological iterative breakthroughs, and expanding market demand" [43]. The profound integration of AI technology with biological system analysis will not only reshape the green bio-manufacturing paradigm for plant natural products, making it more efficient and sustainable, but also give rise to "unnatural" natural products with novel structures and functions. This will open up unprecedented innovation opportunities for drug research and development, functional foods, and green materials, ultimately enabling related industries to achieve leapfrog development and offering transformative solutions to global health, food security, and environmental challenges.

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