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EDITORIAL

# Herb bioprocessing: An emerging paradigm for modernizing herbal medicine

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Processing (Pao Zhi) is a fundamental procedure in traditional Chinese medicine (TCM), indispensable for ensuring the safety and efficacy of herbal treatments in clinical applications. This practice is not only a distinctive feature of TCM clinical application, but also a defining characteristic of TCM as a holistic medical system. TCM processing technology encompasses a comprehensive set of pharmaceutical techniques. It transforms raw medicinal materials into clinically applicable forms. The main forms are decoction pieces (Yinpian) or pharmaceutical preparations. These techniques are based on TCM theory, combined with the intrinsic properties of the medicinal materials. Meanwhile, they align with the specific requirements of TCM clinical practice, dispensing, and formulation. Many TCMs—including toxic ones—need to be applied safely and effectively, and this is critically dependent on this specialized processing procedure.

TCM processing involves diverse methods aimed at modifying compounds to achieve multiple objectives. For example, they enhance therapeutic efficacy, reduce toxicity, and improve taste. However, traditional processing methods often suffer from inherent limitations, including low efficiency, low utilization of medicinal resources, low bioavailability, poor taste, and batch-to-batch inconsistency. Additionally, the underlying mechanisms of processing remain inadequately understood, hindering the establishment of quantitative quality standards for TCM. Thus, modern biotechnology must be leveraged to innovate processing techniques and standardize TCM products-particularly herbal products -using advanced analytical approaches to ensure consistent clinical outcomes.

Probiotic fermentation technology, including solid-state fermentation, liquid fermentation, and bidirectional fermentation, for herbal medicines has developed rapidly to process herbal medicines.[1] This technology enhances herbal efficacy by releasing and transforming bioactive substances, increasing prebiotic/postbiotic components like short-chain fatty acids and functional peptides, and ultimately improving their utilization rate. It has been widely applied in fields including veterinary TCM, feed additives, and functional feeds.[2] In particular, the integration of 'medicine and food homology' materials with probiotic fermentation technology has become a key driver of innovation in the functional food sector. A central mechanism involves the enzymatic conversion of inactive or low active macromolecules into bioactive molecules—such as terpenoids, flavonoids, phenols, alkaloids, and polysaccharides—thereby enhancing efficacy.

Synthetic biology provides foundational tools for modern biomanufacturing, creating novel pathways to produce raw materials for food, pharmaceuticals, and functional ingredients. Within herbal medicine, this technology is overcoming the limitations of traditional cultivation and extraction methods by

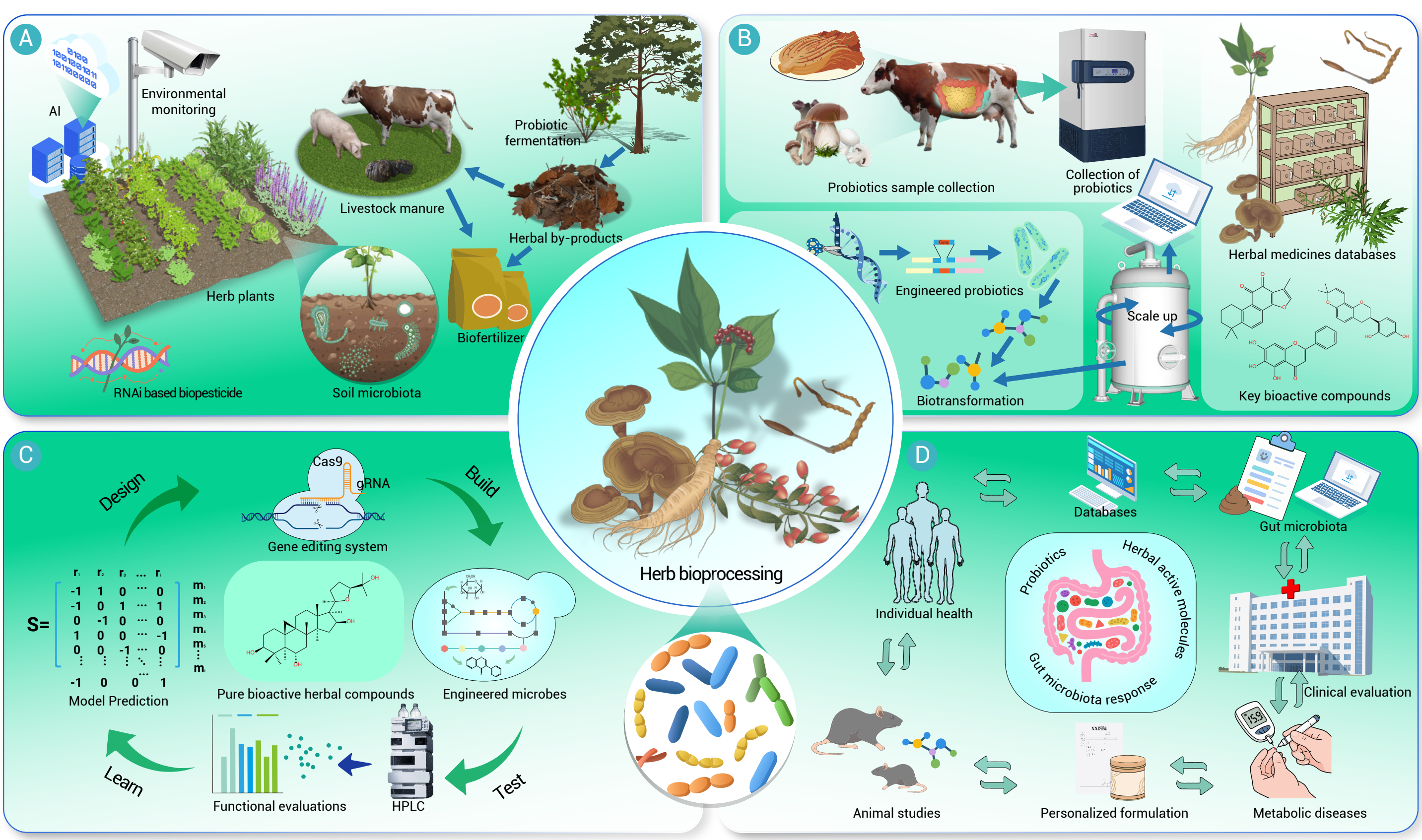


**Figure 1. Schematic illustration of herbal bioprocessing and its applications** (A) Green and sustainable cultivation of medicinal herbs; (B) Probiotic fermentation of herbal medicines is optimized through microbiome data integration and scaled-up biotransformation processes; (C) Synthetic biology enables engineered microorganisms to produce herbal bioactive compounds; (D) Herbal bioprocessing products can be developed into personalized drugs for metabolic diseases, validated through gut microbiota responses and clinical evaluations.

enabling the biosynthesis of various herbal bioactive compounds-such as terpenoids, flavonoids, and phenols-in engineered microorganisms. Strategically formulating these bioactive compounds, either in combination with each other or with probiotic-fermented herbal products, presents a powerful approach to enhance therapeutic efficacy and accelerate the modernization of herbal medicine. Furthermore, these advancements significantly contribute to the conservation of plant resources and reduce dependency on agricultural land.

Based on advancements in probiotic fermentation, synthetic biology, microbiome, and personalized medicine, we propose the cutting-edge concept of 'herb bioprocessing'. This framework aims to integrate advanced multidisciplinary technologies and leverage modern biotechnology to accelerate the modernization of herbal medicines. The core components of herbal bioprocessing include green and sustainable herb cultivation, probiotic fermentation, enzymatic biotransformation, and microbial synthesis of bioactive compounds to create optimized products for application, thereby advancing both herbal medicine and biomanufacturing (Figure 1).

GREEN AND SUSTAINABLE CULTIVATION OF HERBS.The production of high-quality herbs is the basis for bioprocessing. This system implements a green circular economy model to achieve efficient resource utilization and eco-friendly production of herbs (Figure 1A). Cultivation areas are scientifically planned according to herb species-specific growth characteristics, employing strategies like crop rotation and intercropping (e.g., understory cultivation of shade-tolerant medicinal materials) to enhance land-use efficiency. During cultivation, environmental monitoring combined with artificial intelligence (AI) analytics enables the precise delivery of nutrients and microbial agents according to real-time soil fertility and microbiome data. This targeted management optimizes plant growth conditions and soil health and microbiota. Furthermore, the model ensures a closed-loop system. Agricultural by-products, including pruned branches, fallen leaves, discarded plants from cultivation, and fermentation residues, are valorized into livestock feed additives or substrates for high-value crops (e.g., edible fungi).[3] Livestock manure, after composting, serves as high-quality biofertilizer for herbal fields. Biopesticides based on technologies such as RNA interference (RNAi) are proposed to maintain ecological balance and minimize environmental impact. Through establishing this 'cultivation-breeding' circular system, sustainable production of premium herbs is achieved, alongside antibiotic-free feeding of pigs and other livestock using green herbs.

PROBIOTIC FERMENTATION AND ENZYMATIC CATALYSIS OF HERBALMEDICINES. The significant heterogeneity in bioactive metabolite profiles among herbal medicines underscores the value of developing specific probiotic strains for targeted fermentation. This process requires establishing comprehensive databases that document the characteristics of different herbs, including the contents, biotransformation pathways, and efficacy of key bioactive compounds. A plant fermentation strain database can be established using microorganisms isolated from traditional fermented products (e.g., fermented vegetables). Genomic analysis of these isolates would help identify functional enzymes involved in the biotransformation of herbal molecules (Figure 1B). By integrating this genomic information with the characteristics of herbal bioactive compounds, probiotics with optimal fermentation performance can be screened. Additionally, specific enzymes—particularly lignocellulases and certain glycoside hydrolases—can be screened for their biotransformation potential.[4] For molecules that are recalcitrant to transformation by wild-type strains, probiotics can be metabolically engineered to achieve directional biotransformation using these pre-screened enzymes. Ultimately, through the bidirectional selection and combinatorial optimization of herbs and probiotics, this approach enhances therapeutic activity, reduces toxicity, and improves taste (Figure 1B).

PRODUCTION OF HERBAL BIOACTIVE MOLECULES BY ENGINEEREDMICROORGANISMS VIA SYNTHETIC BIOLOGY STRATEGIES. By leveraging multi-omics approaches to reconstruct biosynthetic pathways and integrating microbial synthetic biology technologies, engineered microorganisms have successfully synthesized a range of rare natural herbal products—such as ginsenosides, cycloastragenol, and medicarpin—that occur in low abundance in their natural sources (Figure 1C).[5] Crucially, functional assessments of microbially synthesized compounds remain essential to validate their efficacy and underlying mechanisms. Through iterative design-build-test-learn (DBTL) cycles and metabolic reprogramming, several of these natural products now achieve high production rates, titers, and yields, laying a solid foundation for pharmaceutical development. This approach enables the strategic formulation of multi-component synthetic biology-derived bioactive ingredients either alone or in combination with probiotic-fermented herbal products. Such innovative bioprocessing strategies hold significant promise for developing next-generation herbal preparations with markedly enhanced therapeutic effects, moving beyond the limitations of single-compound drugs like medicarpin and paclitaxel. By ensuring batch consistency, enabling scalable production, and conserving natural resources, this herb bioprocessing strategy amplifies the pharmaceutical value of natural herbs and addresses key challenges in traditional herbal medicine modernization.

OPTIMIZATION AND APPLICATION OF HERB BIOPROCESSINGPRODUCTS. The human microbiome, particularly the gut microbiota, is a critical regulator of health and a key therapeutic target for herbal medicine intervention (Figure 1D). Animal studies are essential to validate the functionality of herbal bioprocessing products and to elucidate the causal relationships between herbal bioactive compounds and health outcomes. Additionally, probiotics can be genetically engineered to enhance their intestinal colonization capacity, enabling precise modulation of the 'probiotics-herbal bioactive compounds-gut microbiota' axis to maximize therapeutic efficacy. AI-driven analysis of individual gut microbiota profiles and health data facilitates the design of personalized formulations, with continuous refinement enabling precise nutritional and therapeutic interventions. These functional bioprocessed products have the potential to improve palatability, enhance therapeutic efficacy, and provide herb-based solutions for public health—particularly in the prevention and management of chronic metabolic diseases such as diabetes and obesity.

Despite the promising prospects of herb bioprocessing empowered by modern biotechnology, several challenges must be addressed. These include: (1) Elucidating the mechanisms and principles that govern the biotransformation of herbal active compounds during bioprocessing; (2) Developing rigorous scientific frameworks to evaluate the efficacy and advantages of herb bioprocessing approaches; (3) Optimizing strategies for the screening, modifying, and engineering of microbial strains for enhanced bioprocessing performance; (4) Establishing comprehensive and quality standards and application benchmarks for bioprocessed herbal products, encompassing critical indicators such as sensory properties, stability, bioavailability, and flavor; (5) Creating an end-to-end research paradigm that integrates synthetic biology product development with functional evaluation to support industrial-scale application. In conclusion, herb bioprocessing represents a transformative framework with the potential to drive innovation across multiple areas, including herbal products, functional foods, cosmetics, and veterinary TCM.

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## AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript.

## DECLARATION OF INTERESTS

Yulong Yin is an Editorial Board member of The Innovation Life and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and the other authors.